Role of Analytical Chemistry in Defense Strategies Against Chemical and Biological Attack

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Key Words

detect-to-protect, prevent-and-detect

Abstract

Analytical chemistry plays a role in the two strategies of defense against chemical or biological weapons that are discussed in this review: the detect-to-protect and the prevent-and-detect strategies. The detect-to-protect method, which is based on detection of a known chemical agent with a specific chemical sensor designed for said agent, has serious flaws. I argue that this approach should be replaced with the prevent-and-detect strategy. Such a change in the defense paradigm would require reallocation of resources, but it is necessary for effective protection of enclosed civilians from chemical and/or biological attack.

1. INTRODUCTION

The sarin gas attack on the Tokyo subway on March 20, 1995, which killed 12 people (1), was not the first deliberate, malicious use of a toxic agent on the general public. One year earlier, the same religious sect responsible for the gas incident mounted a similar attack, in which seven people died. Civilians worldwide are now aware that there exist fanatics who do not abide by the rules of the Geneva Convention and who use any means, including chemical and biological agents, to further their cause. This message was reinforced on September 11, 2001, when another terrorist group used different "weapons"—commercial airliners—to communicate their deadly message. The world will never be the same.

The use of biological weapons dates to the Middle Ages, when invaders tossed the corpses of plague victims over the walls of besieged cities. That was long before the Geneva Convention of 1925, which was formed in response to the use of specially developed chemical warfare agents during World War I. The treaties formulated at the Geneva Convention have been endorsed and honored by most governments. Ironically, however, almost all of the signatories to those treaties have manufactured biological and chemical weapons in large quantities since World War I—"just in case."

In the 1984 industrial accident in Bhopal, India, in which the chemical methyl isocyanate was accidentally released, more than 20,000 people were killed (1). The terrorist attacks using sarin and the anthrax toxin resulted in far fewer fatalities. Yet these incidents' global psychological and political impact has been far greater than that of Bhopal or any other industrial accident. The objective of a terrorist attack is to spread fear and to cause maximum economic harm, not necessarily to inflict the maximum number of casualties. We must bear this in mind when designing effective defense strategies against such attacks.

The response from the scientific community to the new threat has been swift. In January 2002, the National Science Foundation sponsored the first of many workshops (2) and meetings, the proceedings of many of which have been classified. Subsequently, U.S. federal agencies allocated substantial funds to address the threat of terrorist attacks. Similar mobilizations of scientific communities and state resources have taken place in almost all Western countries.

Unsurprisingly, the "detect-to-protect" paradigm emerged as an immediate, almost reflexive, response. The notion that "if it can be detected in time, a protection can be designed" has become the accepted strategy. It has thrust analytical chemistry into a prominent role, which is reflected in both funding and implementation of various detect-to-protect schemes. However, there are fundamental problems with this approach, and alternative means of protection—in which analytical chemistry plays a larger role—should be considered. This review provides a critical assessment of the role of analytical chemistry in such schemes and is broadly based on the report prepared by the National Academy of Sciences (3). The author was the lead member of the subcommittee that prepared that report.

2. THE DETECT-TO PROTECT STRATEGY

There are three reasons that the widely implemented detect-to-protect strategy must fail. Two of the reasons have their origin in the nature of the analytical process itself; the third involves human factors but contains strong analytical elements as well: (*a*) Chemical selectivity directly influences the issues of false positive and false negative results. (*b*) The speed of detection affects remedial action; the release of fast-acting, or acute, agents does not leave much time for an effective response. (*c*) There is an inevitable delay between the reported attack, either false or positive, and the appropriate protective response.

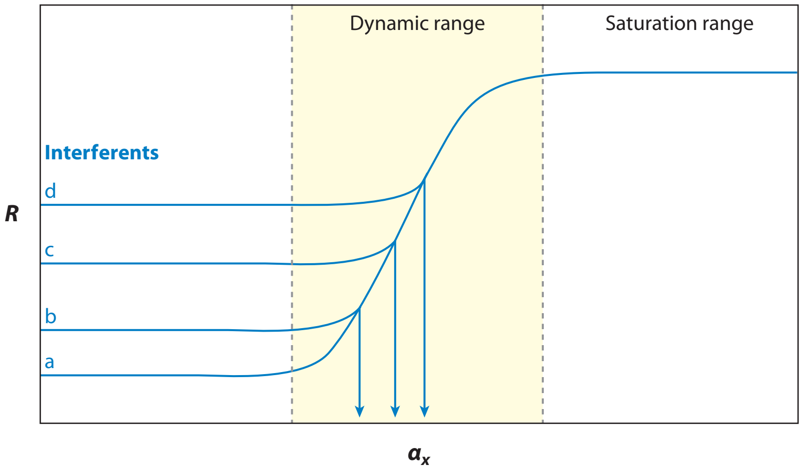

Figure 1

Sample response curves for an analytical method such as a sensor or an assay. Curve *a* represents the response from a sensor tested in a simple medium (i.e., water or clean air), where the only species that elicits a response from the sensor is the analyte of interest. The presence of interferents results in the flat, "no-response" line below the detection limit for the compound of interest. Curves *b*–*d* represent increasing concentrations of interferents. The more complex (i.e., the "dirtier") the sample, the higher the detection limit for the analyte of interest. The effect of increasing levels of interferents is seen in the shift of the detection limit to higher concentrations (α_x) and in the narrowing of the dynamic range. Eventually, the sensor's ability to respond to the analyte vanishes completely.

2.1. Chemical Sensitivity and Selectivity

Any analytical procedure, be it a batch assay or a continuous chemical sensor, can be described by the response curve (**Figure 1**). The curve is a plot of analytical signal against the concentration of the analyte of interest, in this case the concentration of the toxic agent used in a biological or chemical attack (4). At very low concentrations of the analyte, i.e., below the detection limit, the sensor does not respond. The sensor also fails to respond at very high concentrations, when the device becomes saturated. Between the saturation and the detection limits lies the dynamic response range, which defines the usable concentration range of the sensor. The extent of the dynamic range is one of the figures of merit of the analytical method; the wider it is, the better. Although the dynamic response range varies widely for different types of sensors, it depends primarily on the operating environment and on the number and concentrations of interferents in the sample. Even the best chemical sensor can be rendered worthless under conditions where high levels of interferents are present; such conditions affect mainly the detection limit and the dynamic range.

The sensor's ability to discriminate between the species of interest and interfering species is known as chemical selectivity. Arguably, it is the most important figure of merit of a chemical sensor. High selectivity has always been the objective of optimization of chemical sensor designers. The inability of a sensor to respond exclusively to the species of interest causes false negative error, whereas a response to the wrong species results in false positive error. Both errors have dire consequences for the validity of the detect-to-protect scheme, namely no protection and potentially major economic damage. Moreover, consistent false positive responses may lead to the erosion of confidence in the analytical procedure and to the tendency to disregard its results. For instance, who actually pays attention to the official and permanently announced "terrorist threat level orange" at U.S. airports? Such threat qualification and warning have completely lost their meaning. It is equivalent to the proverbial crying wolf.

However, it is possible to develop sensors and detectors that are highly selective for compounds of interest or that are designed for a specific situation, for instance, a sensor based on highly selective enzymatic recognition of the target species: glucose. The glucose sensor is an essential tool for monitoring diabetes. However, this highly selective glucose sensor would be worthless for measurement of urea. Therefore, in order for a molecularly selective sensor to be useful, the identity of that species must exactly match the selectivity of the sensor. Therefore, the identity of the molecule must be known a priori.

A similar argument can be made for a sensor whose function is defined in terms of a specific situation. For example, a smoke alarm detects the presence of smoke, but it does not identify the molecules present in the smoke nor the origin of the smoke. It responds both to a burning house and to burning toast. However, both the house fire and the burning toast require specific action. In the detect-to-protect paradigm, the identity of the agent to be detected or the occurrence of a specific situation must be narrowly defined and matched to the sensor. Otherwise, even the most selective sensor for one toxic agent becomes useless for the detection of another toxic agent.

Recently, U.S. government officials claimed to have knowledge of the nature of weapons of mass destruction, including chemical weapons, that could be used in a terrorist attack against the civilian population. If so, such knowledge would be absolutely essential in the design and proper implementation of chemical sensors in the detect-to-protect strategy. A problem is that there are hundreds of extremely toxic compounds that could be used in a terrorist attack. Therefore, unless the would-be terrorists clearly communicate their choice of toxic agent to the authorities in charge of protecting the public prior to the attack, the detect-to-protect approach cannot be successful. Thus the design, installation, and maintenance of any sensor system designed to detect specific agents probably would not work and would result in an enormous waste of resources. Moreover, it would also lead to a dangerous sense of false security. Unfortunately, molecularly specific sensors for a selected list of chemical agents have already been installed at great expense, both in Tokyo and in some European and American subways.

The solution is somewhat simpler in the case of sensors whose selectivity is defined by situation, i.e., house fire versus burning toast. As with a smoke detector, it is possible to define a useful sensor in toxicological terms. Thus, a positive signal from such a toxicity sensor would indicate the presence of any acutely toxic agent—we would not necessarily need to know its chemical identity. This type of approach has been used in the past by miners, who carried underground live animals that could warn them of the presence of toxins. However, such animals (particularly canaries and white mice) are not considered sufficiently "high-tech" for present-day use. Their electronic equivalents have been proposed (5, 6), but current versions of the "electronic canaries," although conceptually correct, are bulky and expensive to maintain. Combination of living cells with integrated electronics achieves the same purpose (7). Excellent reviews of the subject of broad-spectrum monitoring of environmental toxins have recently been published (8, 9). Those approaches represent a real opportunity to develop miniature biosensors for the detection of life-threatening, toxic substances without needing to know the substances' identity.

In this approach, the longevity of the sensor becomes an important issue. The support of the life of the sensor requires a steady supply of energy and the management of metabolism. For instance, cultures of stem cell–derived cardiomyocytes have been used for pharmacological and toxicological studies (10–12). They are remarkably robust and can remain stable for months. The "beating" of the cells is the analytical signal indicating that they are alive and that the atmosphere is nontoxic. Cessation of the beat indicates cell death and therefore a potentially unsafe environment. Such a device could be implemented in a compact optical sensor (6). The gradual decrease of the intensity of the signal would provide a further measure of analog information; i.e., it could be correlated with experimentally determined LD_{50} toxicity values. It is possible that such an approach can overcome the obvious shortcomings of molecularly specific sensors, as far as selectivity is concerned.

2.2. Speed of Detection

Another strike against the detect-to-protect strategy is more serious but also more obvious. Neglecting this drawback makes the design of a functional defense paradigm more difficult. A released toxin cannot be detected instantaneously. When a toxic agent is released, the offending molecules must travel through space to reach their intended victim. The mode of travel and the time it takes depend on many nonchemical factors, such as the geometry of the physical space, the air flow therein, and the chemical stability and physical parameters of the agent. The toxin's volatility and density relative to air are the most important factors. The efficacy of the toxic agent is the combination of all these factors, and it clearly depends on the conditions of its deployment. Chemical warfare agents such as tabun, sarin, and soman were not designed for deployment in closed civilian spaces; rather, they were developed for and used in trench warfare in World War I. They are highly toxic, much more so than many toxic industrial gases (**Table 1**). However, their efficacy in closed spaces is much lower than that achieved in trench warfare because of their physical parameters. To roughly determine a toxin's efficacy in different release scenarios, multiply the physiological toxicity by the individual relative densities and volatilities. In **Table 1**, the resulting efficacy is shown on logarithmic scale for each agent.

The agent's efficacy also depends on the mode of application. In a "downdraft" application (**Figure 2**), which corresponds to release from a high point, the relative density of the agent is critically important, and the efficacy mirrors the physiological toxicities (**Table 1**). As shown in **Figure 2**, soman is 100 times more effective than phosgene when applied "from the top down." However, volatility is the more important physical parameter for release in a closed space. The logarithm of the product of toxicity and volatility is shown in **Figure 3**. It applies to a point release from a container placed in a low point in a closed space, for instance on the floor. **Figure 3** shows that in this mode of application, chlorine and hydrogen cyanide are comparable to sarin in their efficacy, and phosgene is 10 times more effective than soman. This fact partially

Table 1 Toxicities and physical parameters of relevant toxic agents

Agent	Toxicity relative to chlorine	Volatility at 25 °C ($mg\ m^{-3}$)	Density relative to air
Cyanogen chloride	1	3×10^6	2.0
Chlorine	1	3×10^6	3.0
Hydrogen cyanide	2	1×10^6	0.95
Phosgene	3	4×10^6	3.4
Sulfur mustard (HD)	7	920	5.5
Nitrogen mustard (HN-1)	8	2,000	5.9
Tabun	25	610	4.8
Sarin	100	2.2×10^4	5.6
Soman	150	4×10^3	6.3
Ea5365	250	520	6.8
Tammelin ester	~250	1.4×10^3	5.5

Toxicity values are L_{50} doses, compiled from References 13 and 14. The physical parameters are compiled from References 15 and 16.

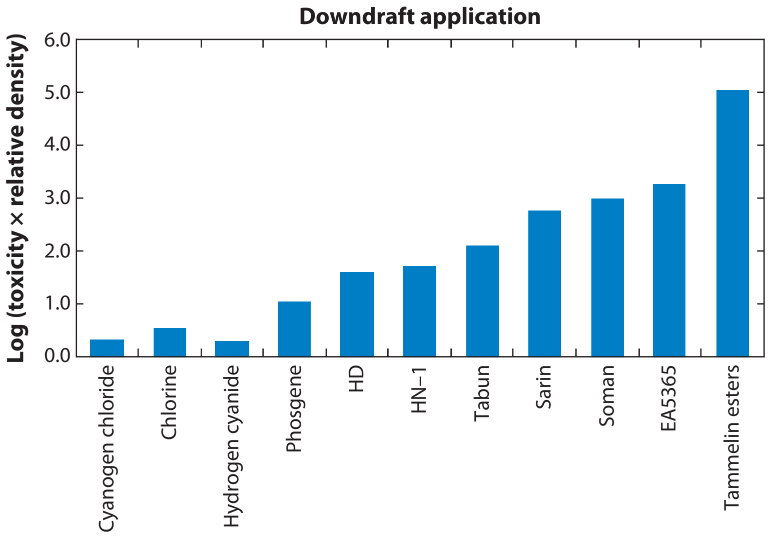

Figure 2

Potency of toxic gases deployed "from the top down." Abbreviations: HD, 1,5-dichloro-3-thiapentane; HN-1, bis-(2-chloroethyl)-ethylamine.

explains the relative failure of the 1995 Tokyo subway attack. Luckily, the containers of the relatively heavy sarin were placed on the floor of the railroad cars, resulting in only 12 casualties and 5,500 injuries. Had the containers been placed in the overhead luggage racks, the result would have been much more devastating. Likewise, the release of an acutely toxic agent through the ventilation system of a closed civilian space would be very serious indeed.

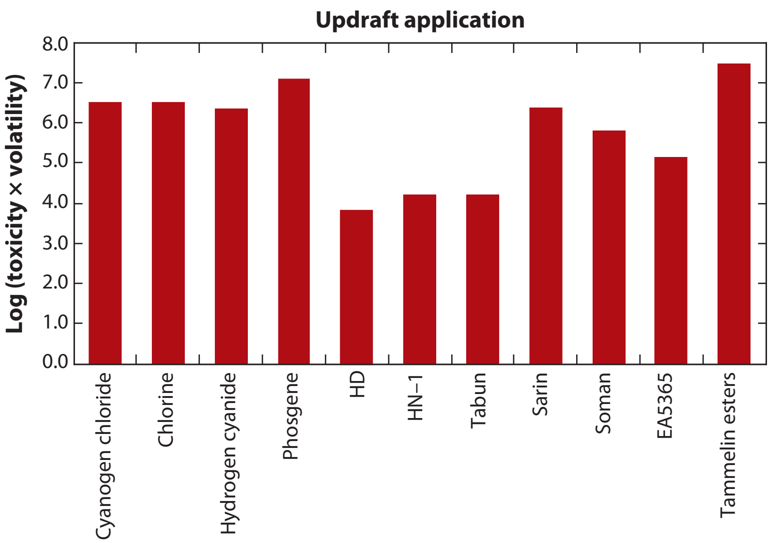

Figure 3

Potency of toxic gases deployed "from the bottom up." Abbreviations: HD, 1,5-dichloro-3-thiapentane; HN-1, bis-(2-chloroethyl)-ethylamine.

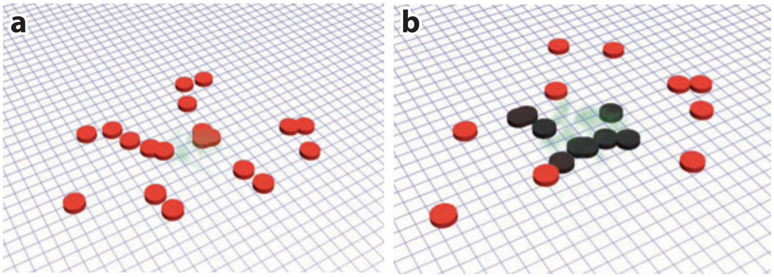

Figure 4

A snapshot of a population of live people, represented by red discs, walking through a point release of a green cloud of (*a*) a nontoxic gas and (*b*) a cloud of acutely toxic gas. The black discs represent the victims.

Regardless of the mode of distribution of the agent and its pathways, the time needed for the agent to reach its victims is the same as the time it takes for it to reach the sensors, which are supposed to warn the would-be victims of the toxin's release. **Figure 4** illustrates two situations in which a toxic gas or a nontoxic gas is released near a group of people. The two scenarios depicted here suggest a fast and accurate mode of detection of any fast-acting toxic gas. The visual observation of the population and the analysis of its behavior patterns become the fastest indications of the lethal attack; thus, the people themselves become the fastest-responding and most accurate indicators of the attack. Obviously, this is not a satisfactory solution to the detect-to-protect problem; however, advance visual observation of the population's behavior patterns could be achieved via installation of video surveillance cameras and pattern recognition software, and this would be less expensive than installation of unnecessary sensors. Sadly, in the Tokyo subway incident, even the most accurate, selective, and fast-responding sensors for sarin or any other toxic agent would not have changed the outcome of the attack.

2.3. Delay in Response

The third—and most serious—problem with the detect-to-protect approach is only obliquely related to analytical chemistry. Nevertheless, analytical chemistry is involved and must be discussed in this context. Let us assume that a sensor for a toxic agent has identified the presence of an unusual gas and has sounded an alarm. Somebody must decide immediately what to do about the alarm given, as the number of casualties will depend on the time delay between the detection of the agent's release and the effective, corrective action. Is the alarm valid, or is it a false positive? Should the ventilation be turned on or off? Should the facility be evacuated, and if so, how? Should sprinklers be turned on?

The economic consequences of emergencies, real or false, cannot be predicted other than that time, effort, and money will be spent to some degree. Shortly after the September 11, 2001 attack, for instance, operations at the Atlanta Hartsfield Airport were interrupted, the airport was evacuated for several hours, and the air traffic in the entire eastern United States was disrupted for many hours. The economic impact of this event was estimated to be tens of millions of dollars. The cause of this event and the ensuing commotion was a passenger who had forgotten his video camera and who had run through the airport exit in the wrong direction to retrieve it. In hindsight, this unusual event was clearly an overreaction on the part of the airport authorities, but their reaction was entirely understandable. There have been many such false alarms that have amounted to major economic loss and overall inconvenience to the general public. With the exception of the anthrax attacks that killed five people in 2002, there have been no verified chemical attacks either on U.S. soil or in Europe or Japan. It is safe to conclude that chemical attacks are possible, even likely, but that their frequency is extremely low. Yet, in the current jittery security atmosphere, protective chemical sensors have been installed in the framework of the detect-to-protect paradigm. Undoubtedly, the terrorists have inflicted incalculable economic damage upon us and have profoundly changed our way of life. That was their goal, and they have succeeded. Is there a rational way to adjust to this threat and to the new parameters of life in the twenty-first century? Can analytical chemistry help?

3. THE PREVENT-AND-DETECT STRATEGY

Delivery of safe potable water to the general public has been one of the greatest accomplishments of public health service; it has become one of the hallmarks of civilization. Importantly, there are similarities between the delivery of safe water to the public and the delivery of safe air to closed public spaces. Nearly every closed public space is serviced by a heating–ventilation–air conditioning (HVAC) system. Its primary functions are to adjust temperature and humidity and to remove particulates by passive filtering. Smaller versions are available for domestic use and are mostly designed to remove particles (see, e.g., **http://www.filters-now.com/**).

A large-scale deployment of HVAC filtering for protection of public places has been the objective of many reports. One report published by the National Institute of Occupational Safety and Health has served as a guide for HVAC installations in public buildings (17). It specifically addresses how to protect civilian closed spaces against chemical and biological attack. It is not known how many such installations have been modified for delivery of clean, sterile air. The identity of these installations is classified, but there are probably many public buildings, such as schools and shopping malls, whose security and technical quality of the HVAC systems are not of this caliber. Also, in places of business such as hospitals, pharmaceutical factories, and semiconductor factories, the emphasis is on removal of particulates; this would protect the buildings' occupants against biological aerosols, but not against fast-acting chemical agents.

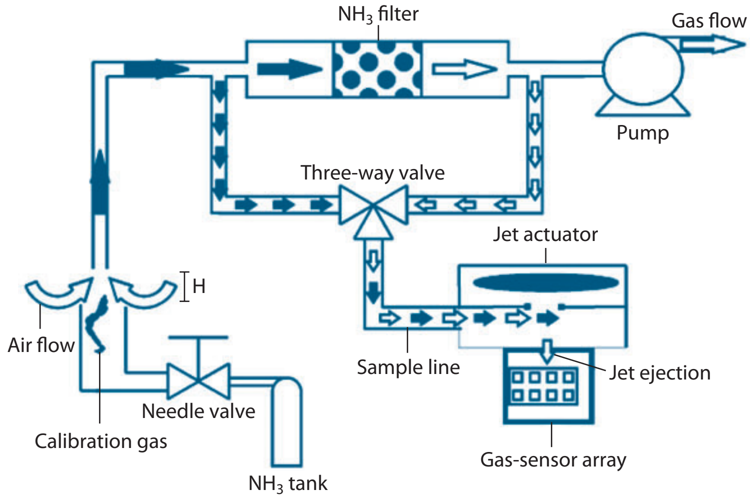

Figure 5

Instrumentation for monitoring air filter status (18).

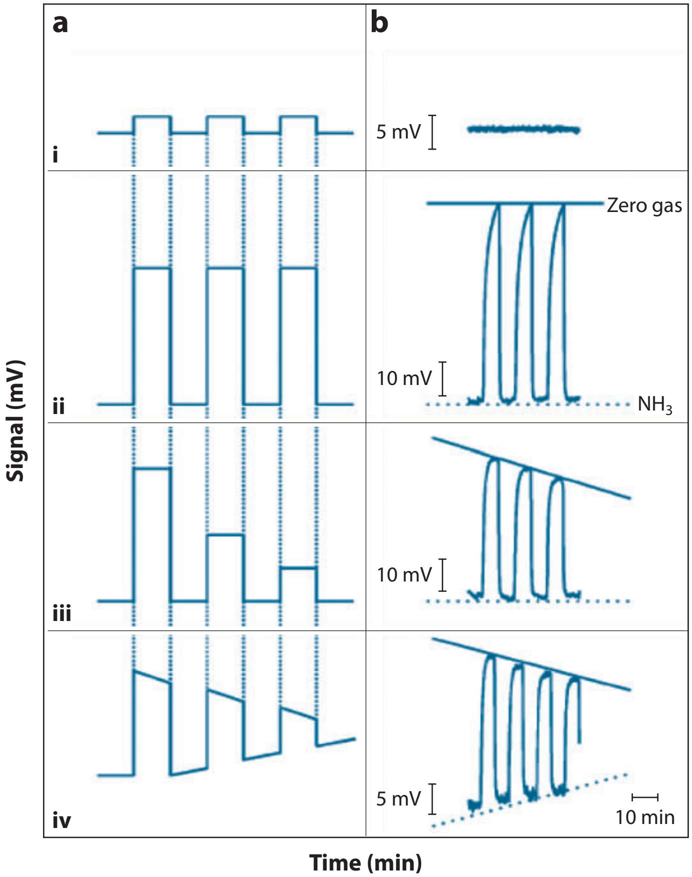

Figure 6

Predicted (*a*) and experimental (*b*) responses of a filter-monitoring system. (*i*) No detectable gas in the air. (*ii*) Detectable gas (NH_3) in the air. Filter and sensors are functioning normally. (*iii*) Shift of the "zero gas" baseline indicates that filter breakthrough has occurred. The sensor may be functioning normally. (*iv*) Both breakthrough and sensors are suspect, and recalibration is necessary (18).

Most filters available today rely on sorption. Relatively few filters use active filtering, in which the toxic agent is rendered harmless by some chemical reaction, typically oxidation. Filters in general have a finite capacity and thus a finite service lifetime. Monitoring of the filter status, namely determining the filter's breakthrough point, is where analytical chemistry can help. The air that passes through a functioning filter is by definition cleaner at the outlet from the filter than at the inlet to the filter. Thus, the outlet air in a functioning filter can be used as the "zero gas," air that does not contain harmful substances, which can serve a dual purpose (**Figure 5**): verifying the status of the filter and correcting for the drift of the baseline of the sensor. A simple diagnostic protocol has been developed that not only determines whether the filter is still active, but also whether the sensor monitoring the system is functioning (18). The scheme shown in **Figure 6** was tested with ammonia gas. Toxicity biosensors (described above) would be the most appropriate choice for protection against acutely toxic, fast-acting agents.

Most acutely toxic agents are highly reactive. This fact can be exploited for their continuous removal via catalytic filters. Likewise, this reactivity can be taken into account when designing

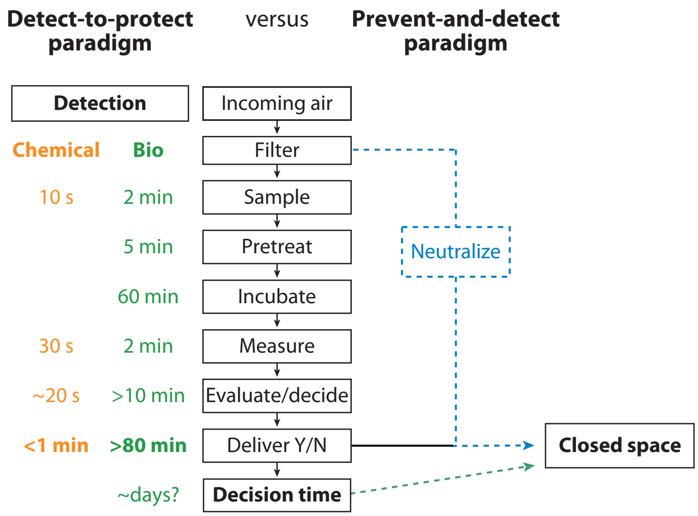

Figure 7

Comparison of the effectiveness of the detect-to-protect and the prevent-and-detect defense strategies. The prevent-and-detect strategy is represented by dashed lines. Delivery of clean air would reduce the reaction time to a biological or chemical attack.

deactivation showers, which may be the fastest first response to a verified attack. Newly developed catalytic filters, supplemented with toxicological sensors, may provide protection against most such agents. There is no detection scheme that is fast enough to serve a similar protective purpose against biological agents. Nevertheless, a plan for large-scale active removal of bacterial and viral biological agents using different available forms of sterilization (such as ultraviolet irradiation, plasma discharge, ionizing radiation, etc.) should be implemented. Active filtering of the air delivered to closed public spaces would serve the same purpose as sterilization of the air in sterile rooms. Just as it is preferable to perform surgeries under sterile conditions than to treat infections resulting from operations performed under nonsterile conditions, it is preferable to deliver potable water rather than treat those sickened by a waterborne, infectious disease. Reducing the spread of common, nonterrorist infectious diseases such as flu would be an additional improvement to public health.

The most important effect of deployment of active filtering would be a dramatic shortening of the reaction time to an attack. It is impossible to quantify this parameter because it depends so much on local conditions, human factors, and the economic impact of the adopted action. Yet decision time is likely to have the greatest influence upon the success or failure of a possible attack and on the number of lives saved or lost.

4. CONCLUSIONS

The two defense strategies discussed above are compared in **Figure 7**, which shows that the detect-to-protect paradigm has three major inherent flaws that make it virtually worthless in comparison with the prevent-and-detect paradigm. Although it is impossible to completely prevent casualties in a chemical and/or biological attack, it is important to minimize the negative impact of such an event, in terms of both human life and economic cost. The tools of analytical chemistry alone cannot accomplish such a task. Likewise, no protective measures can completely eliminate the risk of a successful terrorist attack of any kind. The dominating goal of defense strategies is therefore to decrease the probability of such an attack and to mitigate its consequences if it does take place. A terrorist attack, by definition, encompasses many unknowns, and a successful defense strategy requires a complex systems engineering approach (19). The chemical and nuclear industry has developed sophisticated risk-assessment and safe-operation methodologies. Similar approaches should be adopted by the security industry. It would be wise to invest in development of advanced active-filtering systems and in effective deactivation measures. Analytical thinking, more than analytical chemistry, plays an important role in the preparation of defense strategies.

DISCLOSURE STATEMENT

The author is not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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