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Applying various industry best practices to prevent occupational exposure to hazardous drugs in healthcare

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Applying various industry best practices to prevent occupational exposure to hazardous drugs in healthcare

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Abstract

Hazardous drugs (HDs) have many therapeutic applications in healthcare, but with their benefits come drawbacks. Much has been documented over the past several decades about the adverse effects of HDs, particularly for those with indirect, occupational exposure. This exposure comes primarily from inadvertent dermal contact with drug material and residue, and is observed in individuals who handle HDs directly, including pharmacists and pharmacy technicians who compound and prepare the drugs. However, individuals have the potential for exposure when interacting with HDs at all stages of the drug's "life cycle," including preparation, administration, transport, and waste management. Among various regulatory measures put in place to ensure protection against occupational HD exposure is the relatively recent implementation of USP's chapter <800> Hazardous Drugs - Handling in Healthcare Settings.

Other industries beyond healthcare have their own pertinent hazards and mitigation strategies to prevent the adverse effects of occupational exposure. Exposure hazards like radiation, and other hazardous chemicals such as pesticides, have necessitated the construction of their own unique ecosystems for occupational exposure prevention. Healthcare and pharmacy may benefit from considering the parallels between these fields in order to assess and improve the effectiveness of existing protective measures.

Introduction

Some degree of occupational risk is present in every field. For many healthcare providers - from pharmacists and pharmacy technicians to nurses who administer medications and more - exposure to hazardous drugs (HDs) significantly contributes to their occupational risk. HDs are defined by the US National Institute for Occupational Safety and Health (NIOSH) and include antineoplastic (anticancer) drugs, drugs that pose a reproductive risk for men or women, and drugs that otherwise exhibit "carcinogenicity, teratogenicity or other developmental toxicity, reproductive toxicity, organ toxicity at low doses, genotoxicity, [or] structure and toxicity profiles of new drugs that mimic existing drugs [already] determined hazardous."[1] While HDs are incredibly useful for patients in a variety of clinical situations and have saved countless lives, they also carry an intrinsic risk for those with occupational exposure.

History

In the mid-twentieth century, as a result of studying the effects of mustard gas from World War I on the lymphatic systems of affected soldiers, the first chemotherapeutic HDs began to be seriously studied.[2] It would be only a few more decades until, in the 1970s, some of the first reports of secondary malignancies arose in patients who had previously received antineoplastic drugs.[3] And as early as 1979, evidence was beginning to appear that began to expose the risks that HDs posed to healthcare workers who merely handled the drugs, with one report finding that more than half of studied nurses who treated chemotherapy patients exhibited urine mutagenicity levels higher than office-worker controls.[4]

It was as a direct result of these concerns that the first sets of HD handling guidelines were proposed as potential ways to protect workers from occupational exposure. While there was no widely-accepted standard at that time, in the early 1980s, the American Society of Hospital Pharmacists (ASHP) published "the 1983-84 ASHP Practice Spotlight: Safe Handling of Cytotoxic Drugs" alongside a suggested set of guidelines and a later Technical Assistance Bulletin.[5,6,7] Its note that "the safe handling of cytotoxic drugs is a multidisciplinary concern requiring mutual action by hospitals' medical, nursing, and pharmacy staffs, risk managers, housekeeping supervisors, and others" is particularly prescient for its time.[6] At the federal level, the US Occupational Safety and Health Administration (OSHA) also published a set of recommendations in 1986, which did not contain any mandatory or enforceable standards, but would continue to evolve over the next few decades.[3,8]

One of the biggest steps in the process of standardizing and establishing consistent and effective HD handling standards came with the 2004 "NIOSH Alert: Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Healthcare Settings."[1] This document outlined evidence of worker exposure, aggregated current standards and recommendations, and perhaps most importantly, included a list of what NIOSH considered "hazardous drugs," based on a definition modified from the ASHP guidelines of the 1980s. The NIOSH document provided what would become the standard definition and categorization of "hazardous drugs," which was updated in 2010, 2012, 2014, and 2016, with an additional update currently in process.[1,8] Because of its frequent updates and comprehensive scope, this NIOSH list has become the gold standard for classification of HDs in the United States, as well as in many countries around the

world. However, a standard set of handling guidelines to prevent occupational HD exposure was still lacking.

USP <800>

The United States Pharmacopoeia (USP) was an ideal fit to address this lack of appropriate guidance. USP is an organization that produces and manages many different pharmaceutical standards in the United States, including standards for purity of pharmaceutical ingredients used in compounding. USP also publishes enforceable practice standards in regulatory chapters numbered below <1000>; for example, 2004's chapter <795> provides detailed information on non-sterile product compounding. 2008's chapter <797> does the same for sterile compounding, and until relatively recently, it also included information on both sterile and non-sterile compounding of HDs. However, with time, the need for a separate document to address the complexities and nuance of HDs became clear. In 2016, USP chapter <800> was made available, and after a comment and development period, became official in 2019.[9] USP <800> provides a thorough, evidence-based standard for the protection of product purity and compounder safety that has become the basis of many health systems' HD handling standards in the intervening years.

The standards in USP <800> directly reference the NIOSH list as the guideline to identify hazardous drugs, further reinforcing the eminence of that document.[9] Due to the complexity of the standards involved, health systems are instructed to have a designated person who is responsible for ensuring that USP <800> guidance is followed throughout the entire "life cycle" of the hazardous drug - including shipping and receiving, storage

and compounding, transportation and administration, and cleaning and disposal. The chapter ensures the protection of the compounder from exposure to the product just as much as, if not more than, the protection of the product itself through guidelines for personnel training and personal protective equipment (PPE) and engineering controls. Perhaps even more importantly, USP <800> also outlines an example "medical surveillance program" to monitor and analyze the HD handling patterns and medical assessment data of healthcare workers. These types of programs allow for establishment of baseline and routine assessment and updates to exposure control measures and precautions through monitoring changes in worker health.[9]

As beneficial as USP <800> will surely prove to be in advancing the field, and as far as we have come over the last few decades, we still have much to learn about HD exposure and protection. For a better understanding of the significance of this new chapter and other occupational HD exposure prevention measures, it is best to take a step back and consider the broader picture. To what extent are healthcare workers *actually* exposed to hazardous drugs? Does this exposure vary by occupation, and how? How can this exposure be mitigated, and are those methods effective over time? How is HD exposure commonly measured? Do reliable ways of doing so currently exist? What endpoints (biomedical or otherwise) are most commonly experienced by exposed healthcare workers? What gaps exist in the current body of research and literature, and in our knowledge about HD exposure, and how could they be filled? Finally, what lessons can pharmacy learn from other industries about how best to protect the safety and health of workers? There is a substantial body of evidence highlighting the risks of hazardous drug (HD) exposure, which has led to pharmacies, hospitals, and healthcare systems

already making strides to implement policies and practices to protect employees at risk of exposure to HDs. Further examination is needed to assess the effectiveness of these practices, as well as to propose potential methods of measuring their success.

Hazardous Drugs

NIOSH defines hazardous drugs based on their effects, in an effort to identify drugs that can cause reproductive harm or are carcinogenic, teratogenic, or toxic in some way.[1] By far, the antineoplastic drugs make up the largest category of HDs; these drugs, as the name suggests, are intended to treat and prevent the growth of cancer. Common examples of antineoplastic HDs include cyclophosphamide, fluorouracil, and cisplatin. However, not all HDs are exclusively antineoplastic. Some, like estradiol, are associated with increased risk of endometrial, breast, and ovarian cancer with exposure. Others, such as thalidomide, are teratogens and cause a high rate of birth defects, and still others, like methimazole, are on the list at least in part because of their presence in breast milk.[1] HDs are used for a wide variety of indications, including cancer, and can have very little in common beyond their effects, including on those with indirect, occupational exposure. It is exactly these risks that are of primary concern for many who study them.

Exposure

Some of the risks of occupational exposure to hazardous drugs were known and being studied as early as the late 1970s, but the field is still developing, and more has yet to be learned even today.[4] What is definitely clear, and well-supported by data from the past few decades, is the extent of occupational HD exposure for pharmacists, pharmacy technicians, nurses, and those who prepare and administer hazardous medications. Because of the severity of the risks posed by this HD exposure, studies attempting to quantify and precisely outline those risks are numerous and varied.

Sources of occupational HD exposure can take many forms. For pharmacy workers, the most common exposure risk occurs while compounding and preparing hazardous medications in the pharmacy, most of which require IV admixture before being transported to patients and administered. For example, one study of six antineoplastic compounding and cancer treatment centers found detectable amounts of three studied HDs in 75% of surface samples taken around the pharmacies;[10] another found 52% of samples from 15 hospital pharmacies positive for cyclophosphamide alone.[11] Still another found 45% of hospital pharmacy surface samples were positive for at least one studied HD, with 92% of studied institutions noting contamination.[12] Study after study confirms the presence of HD contamination in pharmacies. Personnel exposure during compounding can arise from aerosolization and unintentional inhalation of droplets containing hazardous drugs, accidental spills, or, in many cases, dermal exposure to powdered or liquid HD material. In fact, as the scientific perspective on HD exposure has changed and evolved over time, the hypothesized primary exposure route has begun

to shift from inhalation to a dermal pathway, reinforcing the benefit of appropriate use of personal protective equipment (PPE) while compounding hazardous drugs.[13]

The occupational exposure risk to pharmacy workers who prepare HDs, or to nurses who administer them to patients, is logical; these workers directly handle the drugs and the administration sets used to deliver the drugs, and therefore are at an obvious direct risk of exposure. However, more and more studies are finding that the risk of HD exposure is significant for workers at *every* stage of the drug's "life cycle" - from manufacturing to packaging and transport, through compounding, internal transit and administration, all the way to waste disposal and cleaning. Particularly given the risks of dermal HD exposure, it is clear that more than a narrow fraction of workers are exposed in these ways. One study, examining a set of six Canadian hospitals, found contamination with cyclophosphamide above the limit of detection in areas not only pertaining to drug preparation and administration but also drug delivery and transport, with more than 500 workers across the six sites potentially exposed, including some with unassuming job titles like "unit clerk, porter, ward aide, dietitian, oncologist, biopacker, and shipper/receiver."[14] Another study of hospital workers found 20% of 225 hand wipe samples were positive for cyclophosphamide (CP), with the highest measured levels coming from a worker with no known CP contact during their shift.[15] This exposure also is relevant to HD manufacturing workers; in another study, workers regularly exposed to air contaminated by chloramphenicol and azathioprine had significantly lower neutrophil counts than controls.[16] Even family members and close contacts of those with direct exposure could be at risk. For example, a case study of two cancer patients found

presence of their chemotherapy drugs in not only the patients' urine, but in that of family members.[17]

The evidence for occupational exposure to HDs is substantial, and as varied as the mechanisms through which the exposure can occur. Certainly contamination arises from the compounding and preparation of HDs, but contamination also arises on the outside of drug vials and shipping and storage containers.[18,19,20] As these drugs are unpacked, retrieved, and transported, the contamination spreads around the hospital or healthcare facility and results in wide-ranging exposure to even unconnected workers. However, questions about the degree of contamination, the severity of contamination, and its clinical relevance are answered primarily through the measurement techniques that have been developed to quantify the presence of HDs.

Measurement

Various measurement techniques have been utilized to support theorized HD exposure with objective data. One of the most commonly used is surface wipe sampling, in which a wipe, often pre-moistened with a standard solvent, is wiped on a specific area and then analyzed with one of a variety of methods (such as liquid or gas chromatography/mass spectrometry). This allows experimenters to quantitatively describe the contamination level as mass of a specific drug per unit area. The biggest advantage of this surface wipe sampling method is its ease of use; once collected, samples may be transported and analyzed in a relatively straightforward manner.[21,22] However, wipe study disadvantages include the cost and the variability involved - the sampling method, and the sensitivity of the test, often changes with each drug studied.[23]

Air samples have also been used to quantify HD contamination, since aerosolization and dispersal of particles are still a risk to workers,[24,25] but again, occupational exposure is currently hypothesized to occur primarily through dermal contact, with inhalation as a secondary route.[26] Other detection methods include measurement of drug levels in the urine or plasma of affected subjects, which are also relatively straightforward samples to collect but have the disadvantage of being reactive, rather than proactive, as an intervention in the case of possible worker exposure.[27,28,29]

All of these measurement methods and techniques are incredibly helpful for quantifying the presence of HD contamination, whether in the environment or already present in healthcare workers. However, a crucial element that is still lacking in many guidelines is a threshold, limit, or target for HD levels in any given environment or system. In the literature, a handful of studies have used observed contamination levels to propose observational "guidance values" for tolerable levels of surface contamination, values under which should be safer for workers.[30,31] In practice, however, the standard that pharmacies and compounding centers adhere to is one borrowed from the radiation field, where workers also need occupational hazard protection - ALARA, or "as low as reasonably achievable."[32] By setting the goal of HD contamination levels as low as possible, the end result is that workers are as safe as possible. However, as time goes on, researchers may discover and further develop more fine-tuned limits and acceptable ranges for environmental HD levels, or for measurements of systemic exposure in humans.

Effects

In an effort to keep track of occupational exposure to workers over time, USP <800> takes a significant step by recommending the formation of a "medical surveillance" program for each health system or other entity tasked with handling hazardous drugs. Medical surveillance programs "involve assessment and documentation of symptom complaints, physical findings, and laboratory values (such as a blood count) to determine whether there is a deviation from the expected norms" in employees who might be at risk of exposure.[9] This USP <800> strategy of vigilance and medical surveillance for the effects of occupational HD exposure on workers is built on studies of the concrete results of such exposure. It involves an initial baseline health assessment for each worker, a review and record of the frequency and degree to which they may be exposed to HDs, and the creation of a follow-up plan for responding to "exposure-related health changes."[9]

These concrete effects of exposure may be difficult to definitively determine. The most common methods involve searching for known physiological adverse effects of the HDs themselves, such as genetic abnormalities and mutations. For example, an extensive 2019 literature review by the US National Toxicology Program found with "moderate confidence in the body of evidence" that occupational exposure to HDs has been associated with genetic toxicity, including "significant" structural chromosomal abnormalities, micronucleus induction, and DNA damage.[33] Through these genetic changes, healthcare workers who are exposed to, for example, antineoplastic HDs may be at an increased risk for cancer themselves.[34] The NTP review also found with "moderate confidence" an association with spontaneous abortion in exposed workers.[33] Other

methods to measure the effects of this exposure, such as quantifying urinary excretion of a hazardous drug or its metabolites, are more indirect; while this approach may be effective in terms of alerting investigators to the presence of occupational exposure, at least a few studies have failed to establish a significant correlation between urine levels and genetic damage, meaning it may not be the most relevant biomarker to consider.[35,36]

An important point to note about these medical surveillance programs, and the biological monitoring that accompanies them, is that they are by nature reactive, rather than proactive. Monitoring workers for exposure to hazardous drugs by measuring the effects HDs have on employees requires that the exposure has already taken place, and that any subsequent biological and/or genetic effects have already occurred. Additionally, while secondary measures of contamination, such as environmental sampling, can serve as a surrogate marker for the likelihood of occupational exposure, this method demands continuous effort to effectively reduce and prevent environmental contamination in order to effectively mitigate occupational exposure for workers.

Mitigation

With such a clear and pressing risk facing healthcare workers who prepare, compound, transport, administer, or otherwise handle hazardous drugs, what has been done to work towards mitigating that exposure? First and most obviously, the use of personal protective equipment (PPE) when preparing HDs has been widespread for decades. USP <800> reinforces this by emphasizing the need for PPE when handling HDs at all stages of their life cycle.[9] These steps are certainly effective, but PPE is only effective when worn properly and consistently. A pre-USP <800> NIOSH survey, for

example, found that 8% of nurses and 10% of pharmacy workers self-reported not always wearing even a single pair of gloves - two pairs are required by USP <800> - when compounding HDs, with comparable usage rates reported regarding other PPE items.[37] A review of twelve studies assessing nurses' use of safe handling precautions found that perceived barriers to PPE use - such as availability of materials, staff workload, workplace safety culture, and education about proper handling methods - also had significant effects on adherence to safety procedures.[38]

However, even when used correctly, PPE alone is rarely enough to completely mitigate environmental contamination and/or occupational exposure to HD materials. Closed-system drug transfer devices (CSTDs) were developed as an additional step to ensure product and compounder protection; the first was FDA cleared in 1998.[39] CSTDs, including products such as PhaSeal™ or EQUASHIELD®, provide a physical barrier to prevent even minor leakage or aerosolization of liquid HD material while still facilitating compounding and administration. While no product is 100% effective, several have been found to be incredibly beneficial. One PhaSeal™ study, for example, found leakage rates when preparing and administering platinum solution to be "3-4 orders of magnitude lower" when using the CSTD, noting additionally that nurses with a broad range of previous work experience were successfully able to adapt to the appropriate use of the device.[40] Another multi-site study concluded that the addition of the PhaSeal™ system to compounding in a biological safety cabinet reduced baseline surface contamination, even to undetectable levels at some sites.[41] A third found a decrease in surface wipe sample positivity rate from 66.7% to 5.8% overall, and from 78% to 2.6% in administration areas, after implementing PhaSeal™.[42] These studies are not outliers, either; CSTDs are

beneficial enough for mitigating HD exposure that USP <800> recommends that they "should" be used for compounding, and "must" be used for administering HDs, "when the dosage form allows."[9]

Individual studies have investigated other methods to mitigate HD contamination and occupational exposure. The centralization of the IV tubing priming process for HD intravenous preparations in the protective conditions of the pharmacy and BSC was effective in one study at reducing floor contamination in patient care areas.[43] In another study, the use of multi-channel, wall-mounted infusion sets for HD administration, as well as self-cleaning toilet seats in patient bathrooms, allowed for better and more regular cleaning of patient environments and resulted in at least a 57% reduction in contamination at various sampled sites.[44] Automated robotic HD compounding has even been studied for its efficacy in preventing environmental contamination; machines such as APOTECAchemo or CytoCare may also be effective at reducing levels of external HD contamination, though the machines themselves may still be contaminated in the process.[45,46] As technology continues to improve, more and better mitigation strategies will surely rise to more common use in HD compounding and administration.

Looking Outward

Beginning soon after the dawn of their use, hazardous drugs have become an increasingly evident risk to healthcare workers who interact with them on a regular basis. Through transport, preparation, compounding, delivery, administration, and waste

management tasks, workers at every step of the medication's "life cycle" run the risk of occupational exposure to substances that are known to pose the risk of serious health effects. This exposure may arise from inhalation of aerosolized particles containing HDs, often created when compounding IV admixtures, but primarily come from dermal exposure to hazardous drug residue from pharmacy surfaces, HD vials, storage or preparation areas, patient excreta, or other indirect sources of surface contamination secondary to ineffective exposure precautions or cleaning methods. Various measurement techniques have been developed to approximate the extent of HD exposure and the effects that they can have on workers, including an increased risk of reproductive harm and genetic abnormalities. As a direct result of increased awareness of these risks, mitigation strategies, techniques, and technologies are in place and being further developed to improve the health of occupationally-exposed workers.

However, gaps still remain in our understanding of the risks posed by hazardous drugs, and there are still areas of research to explore. Simultaneously considering both the health risks of HDs and the difficulty of preventing exposure entirely, is there any tolerably safe level of exposure? Can consistent exposure limits for measurement be put in place, in order to standardize sampling and quantification? Can occupational exposure be proactively measured in order to predict a worker's current risk of adverse health effects, rather than retroactively by analyzing those health effects post-exposure? Broadly, what else can be done to improve the health and safety of healthcare workers occupationally exposed to hazardous drugs? One potential method of answering these questions could be by examining other industries, to assess what parallels may exist

between the methods used to measure, evaluate, and mitigate their workers' exposure to their respective occupational hazards when compared to healthcare fields.

Pharmacy is not the only field that involves regular occupational exposure to hazardous and potentially toxic substances. Many workers interact regularly with sources of ionizing radiation, including other healthcare workers like radiologists and radiopharmacy workers. There are applications for radiation outside of healthcare as well, from nuclear power to sterilization and screening tools. Very broadly, radiation exposure is cause for concern over time at the atomic and subatomic levels, due to the result of abnormal ionization and energy transfer.[47]

The study and utilization of radiation has its roots before the turn of the twentieth century, when scientific figures such as Wilhelm Roentgen, Henri Becquerel, and Marie and Pierre Curie were among the first to document phenomena related to x-rays and radioactivity.[48] The scientific community was also quick to discover some of the chronic adverse health effects of long-term exposure, such as cancers and reproductive sterility. By the mid-1930s, some of the first general conclusions about acceptable limits and values of radiation exposure, both for the average person and for occupationally-exposed workers, were in widespread use. These recommendations evolved over time, as did the organizations presenting them - the UN's International Atomic Energy Agency (formed in 1957) and the US Department of Energy (formed in 1977) among them.[48] During this time, alongside greater and greater knowledge about the potential risks of exposure to radiation came more and more applications for its use in the industrialized world. Many healthcare settings, which already contend with the handling and maintenance of hazardous drugs, are also equipped to deal with radiation via x-ray and CT imaging, and

in some cases, even via radiopharmaceuticals and radiation as treatment for cancer. These healthcare workers, as well as those who use radiation in other contexts, are similarly prepared to deal with occupational hazards, and could inform the handling of hazardous drugs.

Another hazard that many workers encounter through their occupational duties which could provide perspective for healthcare and pharmacy, is exposure to pesticides, used in many agricultural settings as tools to improve yields and simplify preparation of products for sale, or in commercial settings to facilitate pest extermination. These chemicals, including pyrethrins and pyrethroids, organophosphates like malathion and chlorinated compounds such as DDT, can be acutely toxic as well as hazardous over time due to continuous longitudinal exposure.[49]

Pesticides are in no way a new invention; though a relatively recent addition to agricultural practice, some of the earliest known uses of a chemical insecticide were by the ancient Sumerians about 4,500 years ago.[50] Many came from natural sources, such as sulfur, mercury, and arsenic. Another early insecticide, pyrethrum, which is still in use today, was isolated from chrysanthemum flowers for its activity against lice. By the mid-twentieth century, many synthetic pesticides had been developed and were in common use, such as DDT, but their adverse effects were also becoming more and more clear. Famously, the 1962 book *Silent Spring* by Rachel Carson helped draw attention to the environmental and health effects of DDT for both animals and humans, and by 1972, the chemical had been banned from agricultural use in the United States.[51] This evolution of perspective and thought over time has impacted more than just DDT. Concerns over acute toxicity have led to strict controls on PPE and measures for workers applying

agricultural pesticides, for example, while the threat of long-term effects of exposure has led to the development and strengthening of many environmental protection laws. The occupational risk posed by pesticides will also serve as a good example to juxtapose with that of hazardous drugs.

Radiation and pesticides are very similar to each other, and to hazardous drugs, in key ways that are worth investigating. All three hazards are commonly encountered in occupational settings for large amounts of the workforce around the world, and all three pose similar, but distinct, threats to worker safety due to the risk of occupational exposure. Considering the risks, standards of measurement and exposure, and methods of exposure prevention used to protect workers from each of these hazards will be beneficial for perspective when considering the future of hazardous drugs.

Risks and Effects

Radiation does its damage in the form of energy emitted at the atomic level.[47] There are different types of radiation, with different applications and varying levels of intensity, but broadly, the health risks it poses are due to ionizing radiation, the energy of which can damage tissue and DNA when emitted from unstable atoms or other sources. The most energetic varieties, gamma rays and x-rays, have the most power to penetrate the body's surface and therefore to cause the most damage. These damaging effects, most significantly, include a dose-dependent risk of nearly all types of cancer - that is, as degree and duration of radiation exposure increases, the risk of cancer does as well.[52] Due to the nature of the DNA damage, these cancers may not become evident until years

after exposure. This damage can also be teratogenic, leading to an increased risk of birth defects for children of exposed mothers.[47]

While radiation exposure can have adverse health effects when administered in one acute dose (in an extreme example, such as from a nuclear explosion), the vast majority of workers with occupational exposure experience their risk of effects from chronic exposure over time. For pesticides, however, the opposite is often true. Acute pesticide exposure can very quickly lead to toxicity and poisonings; in 2010, over 90,000 poison exposures were related to pesticide use.[49] Exposure may come via accidental ingestion of a pesticide compound, as well as through dermal exposure or inhalation. The most common adverse effects include gastrointestinal distress, such as nausea and vomiting, central nervous effects such as dizziness and fatigue, and potential dermal effects such as contact dermatitis, itching, and redness. However, in rarer cases, pesticides have the potential to cause similar acute adverse effects to radiation and hazardous drugs, including organ toxicities, blood dyscrasias, and reproductive toxicities including low sperm count. This also extends to the chronic effects of even low-dose pesticide exposure over time, which can include neurological problems (including an increased risk for Parkinson's disease) and cancer (including leukemias, lymphomas, and prostate cancer) for the occupationally-exposed worker and for the general population, including children.[49]

Measurement and Standards

Occupational exposure limits for pesticides have been put in place to protect the health of workers. For example, OSHA has set "Permissible Exposure Limits" for a

whole range of pesticides, as well as other chemicals; other organizations, including NIOSH and the American Conference of Governmental Industrial Hygienists (ACGIH) have similar standards.[53] These limits are mostly recorded as measures of concentration of particles in the air (ppm or mg/m3). Devices can analyze those concentrations so that appropriate measures can be taken to either avoid areas of high pesticide levels or protect oneself appropriately during exposure. "Permissible" limits vary based on each individual compound and its potency and toxicity, which can make accuracy difficult when trying to monitor exposure to a wide variety of compounds, but the individualized data are important in order to put together an accurate picture of occupational risk.

Due in large part to the energy involved in radiation exposure, whether acute or chronic, it is relatively straightforward not only to monitor, but to quantify. In fact, a large variety of devices have been developed which are able to detect and/or measure radiation as exposure is taking place; these are referred to as "dosimeters."[54] Dosimeters may measure an individual's personal exposure or broader radiation levels on surfaces or in the environment. Some personal dosimeters may detect exposure in real time, while others need post-exposure analysis to be interpreted. Real-time personal dosimeters may be carried or worn on the body, and may change color, give a numerical exposure reading, or sound an alarm when a dose limit is reached. This variety in devices, purposes, and features allows dosimeters to be an excellent tool for measuring occupational radiation exposure.[54]

Not only is measurement of radiation exposure possible, but there are set guidelines for limits of exposure that have been put in place to protect the health of occupationally-exposed workers. Everyone on Earth experiences various levels of

so-called "background radiation" that occurs naturally, and many people will encounter additional doses of radiation through medical imaging or treatments, such as x-rays.[47] However, these levels of exposure are still far below the limits set by the US government as "acceptable." For example, the average chest x-ray provides a radiation dose of 10 mrem (milli-rem), or 0.1 mSv (milli-Sieverts, the SI unit for radiation), and in 2006, the average effective annual dose per individual in the country was 620 mrem.[55,56] By comparison, the Department of Energy has set a limit of exposure to an annual dose of 5 rems (5,000 mrem) for occupationally-exposed workers.[56] While the ideal standard for exposure limits is still ALARA, "as low as reasonably achievable," in order to protect the safety and health of exposed workers, these guidelines help maintain consistency and perspective when dealing with radiation in the workplace.

Exposure Prevention

The three main principles of radiation protection, and occupational exposure prevention, are time, distance, and shielding.[57] In other words, because the risk of adverse health events due to occupational exposure to radiation is dose-dependent, the best ways to reduce the total dose administered over time are to minimize the time spent exposed to radiation energy, to maximize the distance between the worker and the radiation source, and to ensure that adequate shielding measures are in place to physically protect the worker from the radiating energy. Lead, concrete, and water are good shielding agents, and are often used to contain radioactive materials, but even a lead-lined vest is often used to protect patients who are undergoing x-ray imaging, to help minimize exposure of the x-rays to unnecessary areas of the body.[57] Depending on the nature of the

radioactive source, workers may also use physical PPE, such as gloves, safety goggles, or a respirator, in order to prevent contact with radioactive particles to the skin, face, or lungs. Detailed exposure records are also maintained for occupationally-exposed workers, which allows trends in their exposure levels and health to be tracked and monitored.[54]

One of the most significant sets of regulations for occupational protection against pesticides comes from the US Environmental Protection Agency's (EPA) Agricultural Worker Protection Standard (WPS).[58] These extensive regulations also cover non-chemical risks, such as equipment safety and labor relations, but primarily outline precautions that should be taken to minimize the occupational exposure risk for workers in direct and indirect contact with pesticides and hazardous chemicals. This includes provisions for the public display and availability of information related to the precise compounds being used, as well as where and when they are being applied; adequate safety training, pre-administration checks, and supervision during application; appropriate maintenance and use of PPE for affected workers; and the availability of decontamination supplies and appropriate emergency protocols.[58]

Making Connections

Numerous parallels exist between the three hazards investigated - hazardous drugs, radiation, and pesticides - not only in terms of the occupational health risks they

pose, but also through the ways in which their respective industries have grown and developed to manage, mitigate, and monitor those risks. Whether considering the effects of acute exposure, chronic exposure, or both, each industry has implemented policies and guidelines to prevent adverse health effects for the occupationally-exposed. It is more than likely, therefore, that the healthcare field, and the field of pharmacy, can learn and develop from these parallel industries.

Not only are the risks and potential health effects of radiation and pesticides similar in breadth and severity to those of hazardous drugs, but the effects all three are significant for a much longer duration, and potentially to a broader range of workers, than might initially be assumed. For HDs, this extended risk is seen along the "life cycle" of the drug, from initial manufacturing to transport, through pharmacy preparation and administration to the patient, to waste disposal, maintenance, and more. In the radiation field, the risks are seen primarily as an effect of chronic, low-dose exposure over time, for workers in and out of the healthcare field. And in the case of pesticides, the potential chronic effects range from occupational toxicities to long-term environmental damage. It is this similarity in risks and effects that enables the potential for inter-industrial comparison.

As a result of these long-term risks, comparable standards have been implemented, and capable technology developed, to assess the degree of occupational exposure in each field. Regarding hazardous drugs, this includes the capability to assess environmental contamination via wipe samples, and individual exposure after the fact via biological monitoring. Among the features implemented by the other fields which pharmacy lacks, however, is real-time, quantitative exposure monitoring - for example,

the use of dosimetry in radiation to assess an individual's specific exposure level. Another tool not currently in use against occupational HD exposure is a consistent set of allowable exposure limits, such as those in place for radiation and for pesticides. While the exposure thresholds for radiation are distinguished primarily by occupation, those for pesticides and other hazardous chemicals are unique for each specific compound, due to varying potency and toxicity risks from one to another. Any set of guidelines for HDs would likely do well to include elements of both systems; because of the wide variety of HDs in use, the spectrum of acceptable or toxic levels may also be wide-ranging, and the risk of occupational exposure for employees varies based on job title and duties. All three fields, of course, adhere appropriately to the principle of ALARA, and should continue to do so, but evidence-based exposure guidelines would serve to further protect workers from occupational exposure.

After acknowledging and evaluating the risks of exposure, and quantifying and assessing that exposure for employees, methods of HD exposure prevention should also be further developed in light of these other industries. USP <800> recommends record-keeping over time, including employee health measures at baseline and at regular intervals, for the purpose of tracking changes in health that may be attributed to HD exposure. This is borne out in comparison to the other industries, as well, which maintain health records, or exposure records, or both, in order to be able to properly assess occupational risk. To take further steps towards protection against HDs, further development, alongside further research and data, is on the horizon to evaluate ways to more consistently and appropriately protect workers, including PPE and rates of

compliance, technology such as CSTDs, and new frameworks through which to view previously-collected data.

Recommendations

Having examined these connections in more detail, the overall picture for healthcare and pharmacy is brought into sharper focus. The questions that arose after examining the current state of the industry are more contextualized through subsequent inter-industry comparison. There may not be a tolerably safe limit of exposure to any given HD, but evidence-based guidelines that prioritize the health and safety of occupationally-exposed workers can help us minimize the health risks of HDs, considering the impossibility of entirely preventing exposure. It is conceivable to combine proactive measurement and post-exposure record-keeping when it comes to evaluating and mitigating risk, in order to improve the effectiveness of both. The end result of changes like these, and others that will further health and safety efforts against HD exposure for workers of all kinds, will ultimately include improved patient outcomes, decreased environmental contamination, decreased costs associated with mishandling HDs, and improved employee health and well-being by preventing further occupational HD exposure.

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