Assessment of the Cytotoxic Waste Management in Western Balkan Countries

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Summary

This assessment provides a status report on the Cytotoxic waste management in Western Balkan (WB) countries through utilization of data provided from the International Solid Waste Associations with a focus on National Member countries. For the purpose of the Project, a Questionnaire was developed in order to collect reliable information from the institutions that are generating cytotoxic waste.

WB Countries account for nearly 18 million citizens. It is estimated that around 50000 patients per year are treated with chemotherapy and that approximately 100 tons of hazardous cytotoxic waste is generated throughout the process. Sustainable healthcare waste management presents significant challenges in the countries in transition because of the versatility of hazardous properties. The challenges are mainly related with achieving the necessary standards especially in management of hazardous healthcare waste streams that are generated in smaller rates than the infectious waste but requires very expensive handling and treatment technologies.

In line with collected data, all WB countries have already established similar healthcare waste management systems, in accordance with WHO guidelines and EU directives. Due to the fact of absence of specific treatment technology, the countries are faced with serious issues of not regularly collecting the waste, long term temporary storage and difficulties exporting the waste to countries that poses adequate treatment technologies. These issues can lead to improper storage, treatment and potentially illegal disposal of the cytotoxic waste and increasing the risk toward the public and environment as well.

One of the main founds of this report is willingness for cooperation among the WB countries healthcare systems and institutions in areas such as special investigations and analysis, scientific programs, continuous professional development, transfer of knowledge and practices on various healthcare topics.

The listed recommendations are excellent example on tracing the path for establishing a regional approach for managing of hazardous cytotoxic waste that could serve as a template for international application which could subsequently be utilized elsewhere.
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I. Background

Cytotoxic drugs, while beneficial to patients to treat malignancies, are highly hazardous and may also contain one or more mutagenic, teratogenic, or carcinogenic properties. Cytotoxic waste is associated with cytotoxic drugs which contain chemicals that are toxic to cells. This includes materials, equipment, and residue that are contaminated by cytotoxic drugs. Cytotoxic drugs, also known as antineoplastic drugs, are usually administered to patients with a wide range of malignancies and diseases such as cancer because they prevent the replication and growth of malignant cells, may also be used for the treatment of rheumatoid arthritis and other autoimmune conditions. Since the abnormal cells causing these illnesses grow rapidly and uncontrollably, aggressive medications such as cytotoxic drugs are needed to impair and eradicate them quickly. The range of malignancies will determine the therapeutic procedures as well as drugs and consumables to be used. Accordingly, it is very difficult to assess the amount of cytotoxic waste that is generated during the preparation and delivery of the chemotherapy.

Disposal of items containing/contaminated with these drugs raise serious safety problems, both inside hospitals and after disposal, and should receive special attention.

Healthcare workers may be at risk of being exposed to cytotoxic drugs and its associated waste. Exposure to cytotoxic agents may be through inhalation, ingestion, absorption through the skin or through percutaneous injury. Patients administered cytotoxic drugs excrete bodily fluids that may contain unmetabolized residues and metabolites of the cytotoxic drugs, another source of exposure to healthcare workers.

Poor segregation and management practices may result in a contamination of other waste streams with chemotherapy wastes. Inadequate selection of treatment technology may increase the risk of exposure for treatment and disposal waste workers, because of inhalation and skin exposure of water vapours contaminated with cytotoxic agents. Therefore, the WHO, classifies cytotoxic waste as highly hazardous and should never be disposed without adequate treatment.

The recommended disposal options\(^1\) include the following:

- Return to original supplier
- Incineration at high temperatures
- Chemical degradation

However, there are many countries, that do not possess appropriate treatment Technologies and this waste stream is neglected and disposed improperly, posing high and potentially long lasting risks to human health and environment. Therefore, it is necessary to explore available possibilities for bilateral or multilateral cooperation for handling this particular waste stream, according to International Conventions, National Legislations and the best available practices and technologies.

\(^{1}\) More information about the recommended disposal option are included in the chapter 4
2. Objective/Aim

The main objective is to analyze generation of cytotoxic waste in the Western Balkan Countries, levels of management, and current treatment technologies and potential for improvement. This analysis would then be used for development of national/regional strategies for managing of this particular waste stream.

2.1. Specific objective 1 (PHASE 1)

This project was planned to be realized in several phases. Phase I would be to assess the existing current practices, quantities of waste, and relevant stakeholders/legislation in WB Countries. For this purpose, the ISWA HCW WG\(^2\) reached out to the ISWA national member’s network for local assistance and direct support on national level. For a country that does not have an ISWA National Member, the HCW WG in coordination with the National Members have used private and professional contacts for support in this project and asked for assistance from ISWA RDN\(^3\).

2.2. Specific objective 2 (PHASE 2)

All Western Balkan Countries beside Kosovo, are Parties to the Basel Convention, and based on this it is possible to explore Regional cooperation, together with National supporting regulatory framework of the Western Balkan Countries. That is consistent with the Basel Convention and its Article 11 that allows for bilateral, multilateral and regional agreements or arrangements, notwithstanding the Convention’s general prohibition on transboundary movements between Parties and non- Parties.

<table>
<thead>
<tr>
<th>Participant</th>
<th>Ratification, Acceptance (A), Approval (AA), Accession (a)</th>
<th>Entry into force</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albania</td>
<td>29/06/1999 (a)</td>
<td>27/09/1999</td>
</tr>
<tr>
<td>Bosnia and Herzegovina</td>
<td>16/03/2001 (a)</td>
<td>14/06/2001</td>
</tr>
<tr>
<td>Montenegro</td>
<td>23/10/2006 (d)</td>
<td>03/06/2006</td>
</tr>
<tr>
<td>Macedonia</td>
<td>16/07/1997 (a)</td>
<td>14/10/1997</td>
</tr>
<tr>
<td>Serbia</td>
<td>18/04/2000 (a)</td>
<td>17/07/2000</td>
</tr>
</tbody>
</table>

\(^2\) International Solid Waste Association, Healthcare Waste Working Group

\(^3\) Regional Development Network
Kosovo is not a party to the Basel Convention and given its lack of suitable treatment / disposal facilities, there is a need to export hazardous waste. Its status in the Convention makes this more burdensome than would otherwise be the case, and most likely, must resort to inadequate storage for an indefinite period. Having this in mind as well as the acceptance of the Basel Convention by all its neighbors, it can be expected that Kosovo will accept the Basel Convention agreement in the near future.

By implementing these provisions and multilaterally reviewing them on a regular basis, Regional Cooperation will greatly contribute to the environmentally sound management of transboundary movement of wastes for treatment or destruction.

2.3. Global reference for cancer information

The International Agency for Research on Cancer (IARC) is the specialized cancer agency of the World Health Organization. The objective of the IARC is to promote international collaboration in cancer research.

The IARC has an important role in describing the burden of cancer worldwide, through cooperation with and assistance to cancer registries and in monitoring geographical variations and trends over time.

According the IARC, West Balkans countries follows the European patterns of cancer incidence (left map), however the mortality is higher in WB countries (right map).

Unfortunately, the trends show an increase in the international incidence of cancer in the future. That will have direct impact on the generation of the waste amounts from treatment of cancer patients. The diagram below shows estimated number of incident cases from 2018 to 2040, all cancers, both sexes, all ages.

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4 Data source: Globocan 2018 Graph production: Global Cancer Observatory (http://gco.iarc.fr/© International Agency for Research on Cancer 2018
3. Risks from Cytotoxic Waste

Cytotoxic agents are drugs that result in cell kill and eventual tumor shrinkage, whereas cytostatic agents inhibit tumor growth without direct cytotoxicity. Cytotoxic or cytostatic (CT/CS) waste is produced in reconstitution centers (usually pharmacy departments) and also in small amounts in clinical settings. The waste product can be in original medication containers as well as residue within medical equipment such as tubing and syringes. CS/CT waste is defined as waste that is toxic, carcinogenic, or toxic for reproduction or mutagenic.

Under EU guidance, waste from cytotoxic and cytostatic medicines are grouped together and segregated from all other medicines. These two types of waste have the following EWC codes:

- 18 01 08 - Cytotoxic and cytostatic medicines
- 18 01 09 - Medicines other than 18 01 08

In this Report is used most commonly term, Cytotoxic waste for both categories CS and CT.

3.1. Risk from cytotoxic drugs and waste

Due to their inherent toxicity, high level precautions should be used when handling cytotoxic medicines to ensure patient safety and to prevent occupational exposure and environmental contamination. A safe handling program should be implemented wherever cytotoxic drugs are transported, received, stored, prepared, administered and disposed. To date, persistent weaknesses exist in international\(^5\) and national cancer control programs regarding all aspects related to safe handling of cytotoxic medicines. Unsafe handling practices have been identified in several studies, particularly in countries where access and use of those medicines have recently increased. With the rising burden of cancer and the increased use of chemotherapy treatment, raising awareness on the importance of safe handling of cytotoxic drugs in Low and Middle Income Countries LMIC has therefore become a priority (Grünigen, 2017).

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\(^5\) EU Directive 89/391 - OSH "Framework Directive"; NIOSH, OSHA, OHS UK Guidelines,
The European Union uses the drug classification CMR (carcinogenic, mutagenic, reprotoxic) that is included in a regulation known as the UN Classification and Labelling (CLP/GHS) regulation.

The classification takes into account the level of evidence for the observed CMR effect as shown in table below.  

<table>
<thead>
<tr>
<th>Effects/ Hazard Class</th>
<th>Categories</th>
<th>Category definitions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Carcinogens</strong></td>
<td>Category 1A</td>
<td>Substances known to have carcinogenic potential for humans</td>
</tr>
<tr>
<td></td>
<td>Category 1B</td>
<td>Substances presumed to have carcinogenic potential for humans</td>
</tr>
<tr>
<td></td>
<td>Category 2</td>
<td>Substances suspected to have carcinogenic potential for humans</td>
</tr>
<tr>
<td><strong>Mutagens</strong></td>
<td>Category 1A</td>
<td>Substances known to induce hereditary mutations in the germ cells of humans</td>
</tr>
<tr>
<td></td>
<td>Category 1B</td>
<td>Substances presumed to induce hereditary mutations in the germ cells of humans</td>
</tr>
<tr>
<td></td>
<td>Category 2</td>
<td>Substances of concern because they could induce hereditary mutations in the germ cells of humans</td>
</tr>
<tr>
<td><strong>Reprotoxins</strong></td>
<td>Category 1A</td>
<td>Substances known to be toxic for human reproduction</td>
</tr>
<tr>
<td></td>
<td>Category 1B</td>
<td>Substances presumed to be toxic for human reproduction</td>
</tr>
<tr>
<td></td>
<td>Category 2</td>
<td>Substances suspected of being toxic for human reproduction</td>
</tr>
</tbody>
</table>

### 3.2. Risks to personnel

Beyond patients’ safety, cytotoxic drugs can be a safety issue for the personnel involved in their handling. Concerns about occupational risks for the personnel handling these drugs have been well described in numerous research papers in the literature. References and sources are enclosed in Chapter 9.

The severity of the hazards for health-care workers (HCWs) responsible for the handling or disposal of cytotoxic waste is mainly attributed to its toxicity and the extent and duration of exposure. Exposure to cytotoxic substances in Health Care Facilities (HCFs) occurs during the preparation of, or treatment with drugs or these drugs occurring through inhalation of dust or aerosols, absorption through the skin, ingestion of food contaminated with cytotoxic drugs, ingestion owing to unsafe practices, or from waste items. Exposure may also occur through contact with body fluids and secretions of patients undergoing chemotherapy. Experimental studies have shown that many antineoplastic drugs are carcinogenic and mutagenic and secondary neoplasia is well documented in literature (WHO, 2014). 

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6 UN Classification and Labelling (CLP/GHS) Regulation
Falck and colleagues published first ever evidences of occupational exposure in 1979, by reporting mutagenic substances in the urine of nurses who handled cytotoxic medicines (Falk et al., 1979).

Since then, numerous studies have investigated the potential hazards associated to occupational exposure. Acute and long–term toxic effects have been described. Although there is no strong scientific evidence on whether working with cytotoxic drugs can increase the risk of developing cancer, some direct adverse health effects, such as skin reaction, hair loss and alteration of normal blood cell counts, have been observed on staff where insufficient personal protective measures have been applied (Cytotoxic Drugs and Their waste, 2015)7.

A study from Finland observed increased incidence of spontaneous abortions during pregnancy and malformations in children of females with a history of working with anticancer agents. Similar results were found in studies from Canada and the United States of America. These results were used for prior study demonstrated that exposure of personal cleaning hospital urinals exceeded that of nurses and pharmacists owing to less awareness of risks by lower staff (WHO, 2014).

Many cytotoxic drugs are extreme irritants and have harmful local effects after direct contact with skin or eye, dizziness, nausea, headache, or dermatitis. To minimize the risk of exposure in the different processes, a combination of protective measures should be applied not only regarding healthcare workers (e.g., physicians, nurses, pharmacists) but also other technicians and materials involved in transport, storage, cleaning or disposal of cytotoxic drugs and related waste (Grüningen, 2017).

<table>
<thead>
<tr>
<th>Risk Assessment</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxicity</td>
<td></td>
</tr>
<tr>
<td>Cancerogenic</td>
<td>Chronic toxicity</td>
</tr>
<tr>
<td>Mutagenicity</td>
<td></td>
</tr>
<tr>
<td>Reproductive toxicity</td>
<td></td>
</tr>
<tr>
<td>Irritation</td>
<td>Acute toxicity</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td></td>
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<tr>
<td>Others (nausea, light-head ness)</td>
<td></td>
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<tr>
<td>Dermal Absorption</td>
<td></td>
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<tr>
<td>Route of Exposure</td>
<td></td>
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<tr>
<td>Inhalation</td>
<td></td>
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<tr>
<td>Ingestion</td>
<td></td>
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<tr>
<td>Galenical form</td>
<td></td>
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<tr>
<td>Liquid</td>
<td></td>
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<tr>
<td>Lyophilized powders</td>
<td></td>
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<tr>
<td>Tablets, Capsules</td>
<td></td>
</tr>
<tr>
<td>Aerosols</td>
<td></td>
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<tr>
<td>Handling activities</td>
<td></td>
</tr>
<tr>
<td>Handling drug-contaminated vials</td>
<td></td>
</tr>
<tr>
<td>Reconstituting powdered or lyophilized drugs</td>
<td></td>
</tr>
<tr>
<td>Crushing tablets, opening capsules</td>
<td></td>
</tr>
<tr>
<td>Handling, counting uncoated tablets</td>
<td></td>
</tr>
<tr>
<td>Further dilution of concentrated liquid forms</td>
<td></td>
</tr>
</tbody>
</table>

7 Risk Management Guide for South Australian Health Services
3.3. Risks for environment

Due to the hazard properties of cytotoxic drugs, improper waste management techniques are not only dangerous for staff involved in the process, but environmental contamination might have dramatic ecological consequences and constitute public health threat for the entire community. Careful planning in terms of collection, segregation, storage, transport, and final disposal of cytotoxic waste should not be overlooked. Efforts should be invested to minimize the risks of contaminating water supply and/or soil and allow safe disposal of cytotoxic waste. Incineration at high temperature (>1200°C) or Chemical neutralization through Advanced Oxidation as a new alternative method are the recommended disposal methods, which constitutes a real challenge in many settings as it requires special and very costly and not available technologies (WHO, 2014).

Any discharge of Cytotoxic waste into the environment can have disastrous ecological consequences in the form of persistent land, air, and water pollution.

The list of pharmaceuticals, other hospital-derived chemicals and disinfection by-products present in wastewater and the environment is increasing. Their impacts on human and ecosystem health vary but are becoming more widely understood. In Sweden, the government, universities and pharmaceutical industry are working together to assess and publish toxicological and environmental data, including persistence and bioaccumulation data for pharmaceuticals. This may form the basis of a Europe-wide information scheme and would allow purchasing departments to select products that have reduced environmental effects. The emerging science of “green chemistry” may also lead to new drugs being designed to have the desired curative effects while minimizing adverse environmental impacts (WHO, 2014).

3.4. Generation of the Cytotoxic waste in Healthcare Establishments

All health-care waste management practices seek to implement environmentally sound management of hazardous waste or other waste, best environmental practices and best available techniques in accordance with the Basel and Stockholm conventions and relevant national regulations and requirements. Nevertheless, changes and improvements to waste management practices must be made within the financial and technical capacity of any health-care system. This might include making small, incremental improvements, as well as planning for more significant, longer-term improvements to obtain optimal options, which may only be possible once certain conditions have been reached (WHO, 2017).
About 85% of the waste produced by health-care providers is comparable to domestic waste and usually called “non-hazardous” or “general health-care waste”. It comes mostly from the administrative, kitchen and housekeeping functions of health-care facilities and may also include packaging waste and waste generated during construction and maintenance of health-care buildings. The remaining 15% of health-care waste is regarded as “hazardous” and can pose a number of health and environmental risks.

Poor management of health-care waste exposes health-care workers, waste handlers and the community to infections, toxic effects and injuries. There is also a potential for spreading drug-resistant microorganisms from health-care facilities into the environment through poor health-care waste management. In 2015, a joint WHO/UNICEF assessment found that just over half (58%) of sampled facilities from 24 countries had adequate systems in place for the safe disposal of health care waste (WHO, 2017).

### 3.5. Generation of the Cytotoxic waste

In recent decades an increase in the rate of medical waste generation occurs due to the population growth (Ghasemi et al., 2018; Oweis et al., 2005). Genotoxic wastes are one type of hospital wastes that are extremely dangerous and may cause cell mutation or cancer and their disposal should be taken seriously. Cytotoxic drugs are main component of these wastes. Genotoxic wastes are a subset of hazardous waste that may have mutagenic, teratogenic or carcinogenic properties. This kind of wastes include residues of certain cytostatic drugs are vomit, urine and feces from patients treated with cytostatic drugs, chemicals and as well as low ionizing radiation from materials used for handling of radioactive elements in cancer diagnostics and treatment (Ghasemi et al., 2018; Townend 2001). On the other hand, recent use of

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8 WHO, Safe management of wastes from health-care activities, A summary, 2017
pharmaceuticals and anti-cancer drugs for treating a variety of diseases and cancers are increased, therefore some of these drugs also considered as genotoxic agents. Human exposure to these substances can occur during treatment or among people who work in the medicine production units, nurses and other hospital staff (Ghasemi et al., 2018; Keshava, 1999).

Healthcare waste management includes all activities involved: generation, segregation, transportation, storage, treatment, and the final disposal of wastes which is generated in the healthcare facilities. Experiences shows that Healthcare waste management is often neglected in poor and middle-income countries. Hence identifying the causes and then supporting the improvements of the system are two important key skills that healthcare facility management need for their development (WHO, 2005).

In healthcare facilities that have specialized oncology department and care, genotoxic waste (containing cytostatic or radioactive substances) may constitute as much as 1% of the total healthcare wastes (Capoor et al., 2017). However, the practice shows that the cytotoxic waste represents 5-10% of all hazardous healthcare waste. The quantity of healthcare waste generated varies in different countries and even within in a single country. Healthcare waste production depends on different factors such as the number of hospital's beds, the socio-economic and cultural status of patients, knowledge of workers, the number of customers, and the waste management process (Ghasemi et al., 2018).

Cytotoxic waste includes any residual cytotoxic agent that remains following patient treatment and any materials or equipment potentially contaminated with cytotoxic agents. Generation of the Cytotoxic waste in Healthcare Establishments is related to:

**Equipment**

- Personal protective equipment (PPE)
- Sharps contaminated with cytotoxic agents;
- Disposable equipment contaminated with cytotoxic agents;
- Non-disposable equipment.

**Contaminated linen and clothing**

Clothing and soiled linen may be contaminated with the unchanged agent or an active metabolite.

**Cytotoxic Waste Packaging and PPE**

All cytotoxic waste containers should be sealed prior to collection by hygienic services. Cytotoxic preparations must be transported in sealed designated containers and labelled as cytotoxic waste. Personnel engaged in the routine handling and transport of cytotoxic waste should wear industrial work-wear, polyvinyl chloride (PVC) industrial gloves and safety boots.

Cytotoxic waste should be segregated from other waste streams. Relevant regulations concerning the disposal of cytotoxic waste must be followed.
4. Cytotoxic waste treatment

According to WHO, cytotoxic waste is highly hazardous and should never be landfilled or discharged into the sewerage system. The recommended disposal options include the following:

- **Return to original supplier** – This option is related to the safely packaged but outdated drugs and drugs that are no longer needed and should be returned to the supplier. Although this may be considered as preferred option for countries that lack the facilities for incineration, this practice is considered as far more complicated than initial provision of the drugs because, the outdated drugs are considered as waste and its transport must be handled according to the provisions of the Basel Convention.

- **Incineration at high temperatures** - Full destruction of all cytotoxic substances require temperatures up to 1200°C and this can be applied to all cytotoxic waste. Incineration at lower temperatures usually result in the release of hazardous cytotoxic vapors into the atmosphere. However, there are many countries that do not possess proper modern double-chamber incinerators that will ensure a temperature of 1200°C with a minimum gas residence time of 2 seconds or 1000°C with a minimum gas residence time of 5 seconds will be achieved in the secondary chamber. The incinerator should be fitted with gas-cleaning equipment and it should have an appropriate operating authority from a relevant government body for hazardous waste incineration including incineration of Cytotoxic waste.

Incineration is also possible in rotary kilns designed for thermal decomposition of chemical wastes, in foundries, or in cement kilns, which usually have furnaces operating well in excess of 850°C. Although this is possible from the technology standing point, these facilities must be permitted for treatment of this particular waste stream.

Incineration in most municipal incinerators, in single-chamber incinerators, or by open-air burning is inappropriate for the disposal of cytotoxic waste.

- **Chemical degradation** - Chemical degradation methods, which convert cytotoxic compounds into non-toxic/non-genotoxic compounds, can be used not only for drug residues but also for cleaning of contaminated urinals, spillages, and protective clothing. The methods are appropriate for developing countries. Most of these methods are relatively simple and safe; they include oxidation by potassium permanganate (KMnO4) or sulfuric acid (H2SO4), de-nitration by hydrobromic acid (HBr), or reduction by nickel and aluminium. The methods are not appropriate for the treatment of contaminated body fluids.9

- **Chemical neutralization through Advanced Oxidation using Sodium hypochlorite** is a new alternative method that has already been authorised for treatment of this kind of wastes.

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9 WHO Blue Book. 1st and 2nd edition World Health Organization;
and is based on the principles of chemical oxidation. Modern automated chemical oxidation treatment technologies are an appropriate method, which can ensure real time control and follow-up of the oxidation process parameters and ensure safe release in the environment, with lower operational and investment cost than incineration, WHO10.

5. Methodology of the assessment

One of the core intentions was to involve ISWA National Members in the Project and countries assessment activities. This Project was expected to mobilize and utilize capacities from the National Members. Additionally, it was expected, that their involvement in the project will highlight importance of the members as waste management professional associations in each country respectively.

In the knowledge that Montenegro, Albania and Kosovo do not have ISWA National Members, it was agreed that the existing National Members (MaSWA, SeSWA and BaSWA) utilise their professional connections for collection of relevant and reliable information about the cytotoxic waste management in these countries. Adequate budget from the project was established and made available to existing National Members to cover costs related to data collection from these countries.

Statistical methods have been used to process the data that was collected using a survey. Descriptive statistics methods were used as basic methods for statistical processing of basic data.

For the purpose of the Project, a Questionnaire was developed in order to collect reliable information from the institutions that are generating cytotoxic waste. The request, for the amounts of generated cytotoxic waste in institutions, was for last three years’ period (from 2017 to 2019).

The scope of the research is directly related to data sources, methods, techniques and equipment - and indirectly to hypotheses, indicators and spatial and temporal determination of the research subject. Based on data sources, surveys, more knowledge of the analysis of the current situation has been obtained.

6. Countries Report

WB Countries account for nearly 18 million citizens. It is estimated that around 50000 patients per year are treated with chemotherapy and that approximately 100 tons of hazardous cytotoxic waste is generated throughout the process. None of the WB countries possess sustainable and reliable treatment or destruction methods for this waste stream. Therefore, they are all storing the waste for a long period of time in order to be exported for destruction, or in many cases this waste stream is improperly treated or disposed of in municipal dumpsites which are not

10 WHO “Overview of technologies for the treatment of infectious and sharp waste from health care facilities” 2019
appropriate for this waste stream and is considered to have impact on human and environmental health. In table 4 are presented summarized statistics for Western Balkan Countries which are relevant for the project; the Estimated age-standardized incidence rates in 2018 per 100000 and Estimated age-standardized mortality rates in 2018 per 100000, as well as data about Cytotoxic Waste amounts which are reported in distributed questionnaires.

Cancer incidence and mortality are rapidly growing worldwide. The reasons are complex but reflect both aging and growth of the population, as well as changes in the prevalence and distribution of the main risk factors for cancer, several of which some can be associated with socioeconomic development. GLOBOCAN\textsuperscript{11} estimates of incidence and mortality worldwide for 36 cancers in 185 countries.

<table>
<thead>
<tr>
<th></th>
<th>Estimated age-standardized incidence rates in 2018 per 100000 (GLOBCAN)</th>
<th>Estimated age-standardized mortality rates in 2018 per 100000 (GLOBCAN)</th>
<th>Reported Cytotoxic Waste amounts on Project (tons/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serbia</td>
<td>307.8</td>
<td>150.7</td>
<td>76.2</td>
</tr>
<tr>
<td>Montenegro</td>
<td>221.9</td>
<td>110.6</td>
<td>6.8</td>
</tr>
<tr>
<td>Macedonia</td>
<td>230.8</td>
<td>113.9</td>
<td>22.6</td>
</tr>
<tr>
<td>BIH</td>
<td>220.3</td>
<td>118.9</td>
<td>NA</td>
</tr>
<tr>
<td>Albania</td>
<td>173.9</td>
<td>88.8</td>
<td>NA</td>
</tr>
<tr>
<td>Kosovo</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

6.1. **Serbia**

There is currently no cytotoxic waste treatment facility in the Republic of Serbia. It is expected that Company Remondis from Zrenjanin will put into operation a thermal waste treatment plant (incinerator) after receiving a trial permit in 2020. Current cytotoxic waste management practices include the collection of waste from healthcare facilities by authorized operators and the removal of waste for treatment to Austria or Hungary.

At present, there are 3 major authorized operators operating in the territory of the Republic of Serbia dealing with the storage, transportation and export of medical and pharmaceutical waste, including cytotoxic waste. Also, there are several smaller operators that collect medical waste from healthcare facilities across Serbia, who then transfer it over to one of these 3 larger operators. After receiving cytotoxic waste from healthcare institutions, an authorized operator performs repackaging in ADR\textsuperscript{12} compliant packaging, transports to its warehouse and it is then exported for cytotoxic waste for treatment. Transport of cytotoxic waste is carried out in accordance with the ADR Regulation.

\textsuperscript{11} Global cancer statistics 2018

\textsuperscript{12} European Agreements Concerning the International Carriage of Dangerous Goods by and by Road
Based on the submitted forms of the Dangerous Waste Movement Document, on the portal of the Environmental Protection Agency, filled in by authorized operators that transport and export hazardous waste (Kemis, Miteco, Investfarm Impex doo), it was concluded that in 2018, 76.72 t of cytotoxic waste was exported for treatment. Of the total amount of cytotoxic waste generated, more than 70% are infusion systems, about 5% are sharp objects and about 20% are drug packaging. Data from the Environmental Protection Agency shows that in 2018, out of a total of 328, only 62 health care facilities (including health centers, clinical centers, specialized state and private oncology clinics) submitted an annual report on the types and quantities of medical waste generated. Based on these data, a total of 31.3 tons of cytotoxic waste was generated in 2017, while in 2018 this amount increased to 40.1 tones.

6.2. Montenegro

The National Strategy for the Management of Medical Waste of Montenegro has classified the medical waste according to the national classification scheme, according to which cytotoxic waste falls into the category of medical waste requiring special treatment, i.e. into category B4 - possess a potential risk to persons handling it (carcinogenicity, mutagenicity and teratogenicity) and must be eliminated according to a special procedure.

The quantities of cytotoxic waste generated in Montenegro were obtained on the basis of data from the Medical Waste Management Plan for Montenegro for the period 2016-2020 and amount to 6.88 t annually. According to this plan, the largest share of hazardous medical waste generated in public health institutions is infectious waste (80%), followed by sharp objects (8%), chemical waste (5%), pathological waste (3%) and finally pharmaceutical waste and cytostatics with cytostatic contaminated packaging (2%).

The current practices related with cytotoxic waste management in Montenegro are based on the sorting of waste at the point of origin, temporary storage within the institution (maximum 12 months) and handing over to an authorized operator. The packaging used for the packaging of medical waste is sorted by color on yellow (infectious medical waste), brown (waste for burial or cremation), and when referring to cytotoxic waste, red packaging is used for hazardous waste, i.e. a locked pharmacy box and special containers labelled "Dangerous from the Pharmacy". Transport of medical waste from the temporary storage of health facilities is carried out by an authorized operator, who has an appropriate permit for export abroad for early treatment.

6.3. Macedonia

According the National Legislation and the Rulebook for Healthcare waste management from 2007, cytotoxic waste is identified as separate healthcare waste stream and is being treated as such. There are 3 public and one private institution that are generating cytotoxic wastes, however the biggest one is the University Clinic for Oncology and Radiotherapy in Skopje. According to the official reports, for 2018, around 22.638kg have been generated in this institution. It is
Assessment of the Cytotoxic Waste Management in Western Balkan Countries

estimated almost 90% of the patients are treated in the University Clinical Centre in Skopje. However, it is important to say that this amount refers to all healthcare waste that is generated in this institution, including infectious waste from their biochemistry laboratory, as well as from the preparation of the chemotherapy and application of the same.

The Cytotoxic waste is segregated as separate stream at the hospital level, however, it is stored in same storage with infectious waste. Upon collection it is collected with same vehicle for hazardous waste in bulk. The whole amount is measured as medical waste and sent to incineration at the incinerator on Drsila landfill in Skopje.

This incinerator represents the only licensed facility for the cytotoxic waste in Macedonia, however due its deteriorated condition, it has been a subject of massive negative publicity in the last eight years. Beside the incinerator in Drisla, there is one more private licensed facility Eko Klub, however it is only permitted to treat infectious waste where it is decontaminated by autoclaving.

It is agreed with management of the Clinical Centre to conduct a trial measure of the volume of waste generated during the preparation and administration of the chemotherapy.

6.4. Bosnia and Herzegovina

Bosnia and Herzegovina is a complex federal state with confederate elements; it consists of two entities - the Federation of Bosnia and Herzegovina and the Republika Srpska and the Brcko District. The management of certain issues, including waste, is the responsibility of the entities. So, there are “duplicate” Laws and Regulations concerning the management and waste from healthcare institutions.

In Bosnia and Herzegovina, health services are provided in 28 hospital-type institutions, 17 of which are located in the territory of the Federation of Bosnia and Herzegovina, 10 are located in the territory of Republika Srpska and 1 in the territory of the Brcko District. The questionnaire was sent to all institutions. Out of 28 institutions, 5 did not provide data and responses and 11 responded to state that they produced cytotoxic waste.

In Bosnia and Herzegovina, there is legislation dealing with the management of cytotoxic waste, and most health care institutions that produce cytotoxic waste are aware that there is a legal framework, however, they are not aware of what legal acts are. Almost all establishments use internal policies to manage cytotoxic waste, and from the responses we can see that the acts are not the same in each institution and they are leading to a different interpretation of how this waste category is labeled, stored and disposed.

Almost all establishments recognize cytotoxic waste as hazardous waste, and that there is a legal basis for the appointment of responsible persons as well as for their professional training. In all institutions, however, there is no continuing education and no education plan, which can lead to improper handling of this waste category, as well as endangering the health of staff, patients, employees of the health care institution and the local population.
In Republika Srpska, institutions are required to submit a report on waste quantities to the Environmental and Energy Efficiency Fund, while in the Federation, reports are not submitted on a regular basis. Few healthcare institutions keep records of the amount of cytotoxic waste, and it is therefore difficult to reach the total amount of cytotoxic waste produced in Bosnia and Herzegovina. Cytotoxic and cytostatic therapy is mainly administered in public health facilities of a hospital type, with the exception of one private health facility in Banja Luka.

Only one institution is aware that very small amounts of cytotoxic waste is also generated in veterinary facilities.

In most institutions, cytotoxic waste is separated, packaged and characterized as a separate waste stream. The problem is that there is no harmonized legislation on packaging colors, and transport so the staff are not familiar with how to safely transport and store this category of waste.

There is no technology for cytotoxic waste treatment in Bosnia and Herzegovina, and most institutions use third party services for the transportation, storage and export of cytotoxic waste. They have valid licenses and permits to carry out this activity. Hospitals, generally, contract the third-party services for the collection, transportation and storage of cytotoxic waste for a period of one year.

Waste is taken from hospitals on a dependency basis from institution to institution, every 15 days, and monthly up to twice a year. Hospital facilities are not sufficiently aware that there are more operators in the territory of Bosnia and Herzegovina who have the necessary permits to dispose of cytotoxic waste.

6.5. Albania

Healthcare waste management in Albania is regulated with specific guideline issued by the Ministry of Health. Each hospital is obligated to develop an internal waste management plan and should contract operators for collection and disposal of the waste if they do not possess appropriate treatment technology. The law on Waste 2003 in Article 18 Processing and elimination of hospital waste states that Processing and elimination of hospital waste is carried out through incineration in specially designed establishments and that the Minister of Health and the Minister of Environment approve the regulations for processing and elimination of hospital waste, as well as criteria and rules for the installation and operations of incineration establishments. In 2011 Albania’s Health Ministry distributed seven hydro-claves to hospitals and other medical institutions, including this one in Tirana, as part of a World Bank Project.

Cytotoxic waste is identified as separate waste stream that is generated during the preparation and application of chemotherapy. There are 3 companies that are licensed for waste collection and export. One of them is Polyeco, a company with solid reputation and pedigree. The waste is usually collected and exported to Greece for storage and further incineration in specific EU countries.
According the EEA Albania country fact sheet 2018 identifies that healthcare waste management is a segment that needs to be improved. Additionally, there are no licensed waste incineration facilities and it is common to burn household and other waste in the open.

6.6. Kosovo

Kosovo is not a party to the Basel Convention and given its lack of suitable treatment / disposal facilities, there is a need to export hazardous waste. Its status in the Convention makes this more burdensome than would otherwise be the case, results in the inadequate storage of waste for an indefinite period. In addition to current waste generation, there is also a need to manage legacy wastes of a hazardous nature, a result of past industrial activities. More positively, there is a good example of bilateral cooperation according the Agreement on shipments of waste generated by the KFOR/NATO troops from Kosovo (Serbia and Montenegro) to the Federal Republic of Germany from 2000.

Healthcare waste management in Kosovo is regulated with Administrative instruction for management of Medical Human and Veterinary waste No 22/2013. This administrative instruction is identifying and defining all healthcare waste types and the activities and procedures related with their management. It is important to mention that Cytotoxic waste is not defined in definition chapter, however it is identified as a sub stream of hazardous medical waste under point 5.4 as cytotoxic, cytostatic and insecticides. Article 8 identifies the packing and color coding of the healthcare wastes streams. However cytotoxic waste is not precisely identified in this chapter.

This can lead to potentially inappropriate identification and mixing of the waste streams. There are other articles in the instruction which are not specifically in line with the WHO recommendations and best practices.

The healthcare institutions are obligated to develop internal plan for healthcare waste management according the mentioned instruction. Both biohazard and Cytotoxic hazard symbols (labels) for identifying the healthcare waste are used, so this means that infectious and cytotoxic waste can be mixed and treated together.

The Environmental Agency in Kosovo is responsible for collecting all data related to waste generation and movement and all generators are obligated to present an annual report. According to the annual report on state of the environment in Kosovo from 2017, the medical waste is treated in 8 plants, located within the main hospital centers in Kosovo.

Based on the data collected by KEPA, it is noted that the treatment of such wastes is increasingly growing from year to year (481,375.00kg in 2015, 522,645.80kg in 2016 and 532,323.11kg in 2017). This report considers that not all health institutions dispose waste for treatment in permitted facilities otherwise the amount of these waste would have been increased.

The country fact sheet from 2018 issued by European Environmental Protection Agency, states that some small incineration plants are burning without generating energy, aiming to reduce the amount of infectious waste and open burning of wastes at illegal landfills. During the project
progress, no relevant information was provided that the cytotoxic waste is separately managed and exported from Kosovo on proper incineration.

According the information presented to the project, there are 3 licensed companies in Kosovo for export of waste. However only subsidiary of Greek Environmental Protection Engineering S.A. was identified.

7. Cytotoxic Waste Stream Assessment

7.1. Rationale

The administration of chemotherapy is a complex process where depending on the type of pathology, chemotherapy can involve usage from one to five different cytostatic medicines including medicines that will relieve the side effects of the cytotoxic treatment. The pattern for application/administration of chemotherapy is different from patient to patient depending on the patient condition and needs. That means that the one chemotherapy treatment may include three to five infusion bottles, with different solutions and volumes.

7.2. Methodology of the assessment

The waste is generated in two places, chemotherapy preparation room and in a patient or dedicated administration room. During the preparation, waste that is generated is usually packaging - the primary packing (ampoules and or vials), needles and syringes, special plastic adapters, PPE (gloves, aprons, masks etc.). The preparation is done in safety cabinets or isolators in order to prevent exposure of the staff on cytotoxic evaporations and fumes. All waste generated here is considered cytotoxic waste.

Depending on the type of the therapy and patient, the therapy can be provided daily hospital in a period of few hours, however the application sometime can last more than 24 hours. Usually the IV cannula is applied to the patient and the IV solutions are changed depending on the type of chemotherapy. If the application is planned to be applied in period of more than 24 hours, the chemotherapy is applied via infusion pump. The waste that is generated is usually IV sets and bottles, gloves and skin disinfection material. In order to reduce the cytotoxic waste amounts, it is considered the cytostatic agents are diluted and beside the trace contamination of the bottle and IV sets, this waste is considered as infectious.
The measurement was agreed with the organizations to be conducted in such a manner as not to change their standard operating procedure and patient comfort during the chemotherapy. It was also agreed with the workers to perform everyday working routine, so the results represent current practices and waste amounts. It is important to mention that the period was involving series of national and religious holidays. Since the therapy is scheduled, many of the patients scheduled their therapy according their holydays schedule and this issue affected the overall number of patients.

7.3. Results from the Measuring

For the purpose of the precise assessment, measurement of the cytotoxic waste was performed in 3 institutions: A regional clinical center, clinic for oncology and secondary hospital. One of the criteria, to have better assessment, was to involve patients of different pathology and age groups as well as different administration schemes. The selection of different institutions was intentional so the results will represent generation of waste at different healthcare levels.
The assessment involved measuring of waste quantities that are generated during chemotherapy administration to 185 patients in 3 institutions. Total waste collected that was 58.58 kg or 25.85 kg from the preparation of the chemotherapy and 32.73 kg from the application of the same. If comparing the results, the results varied from 0.36 kg per patient in Bosnia and Herzegovina, to 0.33 kg in Macedonia and 0.25 kg in Serbia. As average value of cytotoxic waste per patient is considered 0.32 kg or 0.14 kg from preparation and 0.18 kg from application of the chemotherapy. The table below contains results from the measurements in average values.

As usual practice requires, the containers of waste were assessed to determine contents and quality of the segregation. The waste contents focused on specific items like glass (ampoules and vials), plastics (IV bottles and sets) and used PPE (gloves, masks, cleaning and absorbent materials etc.). Because the sharps were generated in small amounts, the quantities were added to the PPE amount. Results are presented in the table and diagrams below.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Generated Waste (kg)</th>
<th>Waste per stage (kg)</th>
<th>Waste Per patient (kg)</th>
<th>Waste per patient per stage (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>185</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ampoules and Vials (Glass)</td>
<td>22.8</td>
<td>25.85</td>
<td>0.12</td>
<td>0.14</td>
</tr>
<tr>
<td>PPE and Sharps</td>
<td>3.05</td>
<td></td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>IV Bottles (Plastic)</td>
<td>24.35</td>
<td>32.73</td>
<td>0.13</td>
<td>0.18</td>
</tr>
<tr>
<td>IV sets (Plastic)</td>
<td>8.38</td>
<td></td>
<td></td>
<td>0.05</td>
</tr>
<tr>
<td>Total amount</td>
<td>58.58</td>
<td></td>
<td>0.32</td>
<td></td>
</tr>
</tbody>
</table>

As it can be noticed, most of the concentrated cytotoxic waste is generated during the preparation of the chemotherapy, taking into account that the chemotherapy medicine is diluted in the systems for application of the same.
As indicated in the above diagrams, it can be noticed that the cytotoxic waste (CW) is consisted of primary packaging glass vials and ampoules, plastic single use items as syringes, tubes and various PPE and materials for hygienic maintenance. Primary packing glass can be considered as, the most hazardous, due to the concentration of residual matter. It is generated in smaller volumes, but with high weight because of the weight of the glass. It is considered as separate waste stream and usually it is not mixed with the other waste streams (plastic bottles and IV sets).

8. Conclusions and Recommendations

8.1. Legislation

The EU directives, as well as provisions of the international conventions (Basel, Stockholm, Aarhus and Minamata conventions), are implemented in the National legislation frameworks in all countries. All countries have developed National bylaws related to healthcare waste management and the main provisions are implemented at the institutional levels. Cytotoxic waste is separated as individual waste stream and handled in accordance with established practices.

All countries, beside Macedonia, the cytotoxic waste is being exported by licensed companies, for destruction by permitted incineration, however on occasion the waste is exported for additional temporary storage until it is consolidated with other waste and re-exported for incineration. This means there are situations where waste may be stored longer than 12 months before it is removed and destroyed in a licensed facility somewhere within the EU.

Although the legislation is in place, it is common practices that the legislation is not entirely implemented or certain technical or operational capacities, allowed by the legislation is not exploited entirely or up to their full potential.
8.2. Institutional organization

The level of practical implementation is different in all countries depending on the internal resources and capacities. The complexity of the notification process for obtaining a permit for export of hazardous wastes, as well as the slow reactions from the authorities is recognized as one of the main concerns. This influences the duration of the whole process of export of the waste and extends the period for storage of this waste in the countries.

All countries have Basel Convention Focal points however these focal points are mainly dealing with operational issues related with it. There is low operative capacity for exploitation of potential for international cooperation under the Basel Convention provisions. The cooperation between the focal points is mainly in relation of obtaining transit permits.

Institutional development is generally a very slow process and usually takes a lot of time and effort and also depends on the political will in the countries, which is not always present. The response from the Regulatory bodies and Authorities is usually very slow and that is mainly related with lack of administrative, operational and technical capacities. Due to these constraints, they are using their resources almost entirely on operational issues and not on development, improvement and upgrade of the institutional development.

8.3. Operational organization

Each generator of the cytotoxic waste is responsible to select and contract licensed company for handling of this waste and to export the waste to a treatment facility with whom they have. Taking into consideration the number of generators and licensed operators, that means that there are a lot of generation points and subjects that operates in this segment which makes it complex and difficult to monitor and control. (see Situation 1 below). In the existing system there are many entities that have responsibility to report the generated wastes to the relevant authorities.

Before inland transport to the intermediary storages, the waste is being analyzed, identified, packed properly and the packs are labelled. The waste is stored in licensed storage facilities, however, there are situations where the storage conditions are not adequate for long term storage of this waste stream.

Once the notification process started, the waste is labelled, containerized onto pallets or IBC’s and loaded in presence of a licensed Dangerous Goods Safety Advisor (DGSA). The Customs authority will confirm that all conditions are fulfilled for the load to be exported. The waste should be securely stored until an export permit is issued by the relevant Authorities.
8.4. General recommendations

Understanding that cytotoxic waste is managed at an institutional level and considering that chemotherapy service is mainly provided in public health institutions, it will be beneficial to explore possibility to establish organizational coordination department, within the existing capacities, that will deal with the waste within the healthcare system. This department would collect all information related with waste handling as well as will be able to coordinate export of the hazardous wastes in the region. They will contract nationally reliable and licensed operators who will have the role of collection from the individual generators, manage central waste storage and will apply for export permit. The waste coordination departments can cooperate with their counterparts in the region in order to consolidate stored amounts of hazardous wastes and organize consolidated shipments which will be more effective and economically affordable. By doing so it will reduce the possibility for the waste to be subject of long-term storage and other handling issues related with it (see Situation 3 below).

Having the network of Coordinator departments established it is to be expected that this network would be able to control the management of other hazardous wastes that are generated in the healthcare systems on national and regional level. This will ensure that the hazardous wastes are correctly collected, identified and packed, stored and exported for proper destruction.
For this purpose, it would be necessary to cooperate with the local Regulators in the process of exploiting existing legal and regulatory opportunities that will influence improvement of the administrative, operational and occupational health and safety practices.

Once similar practice is implemented in the neighboring countries in the region it will be possible to sign bilateral/multilateral agreement for operational cooperation in the exporting of the cytotoxic waste.
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