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Green Nuclear Medicine and Radiotheranostics

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There is a significantly growing interest in diagnostic and therapeutic radiopharmaceuticals, and it is foreseeable that an unprecedented number of patients will need to be treated with new nuclear medicine therapies. This predicted increase will have potentially significant environmental impacts. In this discussion, we show different areas of impact, as well as possible measures to reduce such impact. These measures may impact areas from the entire supply chain, starting at the production site of medical isotopes, the energy supply needed for production, transportation, and adaption of the injected amounts of radiopharmaceuticals in clinical use. Furthermore, arguments of local versus centralized production, potentially increasing or decreasing nuclear medicine procedures versus other greenhouse gas–emitting medical imaging tests, as well as radiopharmaceutical waste handling implications, are summarized and weighed against the current status. Overall, this summary hopefully serves as a basis for further discussion in the nuclear medicine community, potentially increases awareness of the environmental impact of this exciting medical field, and may even lead to implementation of measures.

Key Words: molecular imaging; radionuclide therapy; radiopharmaceuticals; green nuclear medicine; radiotheranostics; health economics

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The nuclear medicine community and the isotope production sector are currently experiencing an unprecedented increase in interest, investments, and production capacity. Thus, the medical community needs to consider production, supply chain safety, and the environmental impact of this field. In this overview, we debate and provide a basis for discussion about how nuclear medicine could help to support an environmental transition, reduce ecologic impact, and preserve resources in diagnostic and therapeutic nuclear medicine, and we discuss possible (and hopefully controversial) measures to mitigate possible adverse effects.

THE INCREASING RADIOPHARMACEUTICAL MARKET

Therapeutic radiopharmaceuticals have seen markedly growing interest from the classic pharmaceutical industry, resulting in an increasing number of new molecules under development with blockbuster potential. The nuclear medicine market is anticipated to grow from an annual $9.3 billion in 2023 to at least $42 billion in 2033, with an anticipated yearly growth of 29% over this period for therapeutics alone (*1*). This includes new indications for treatment, extension of the application with the same molecules, and the large Chinese market, which potentially will see millions of patients imaged and treated by 2032 (*1,2*). Thus, there is a need for more treatment capacity, experienced staff, and equipment, with consequently increasing logistic needs and more waste.

GENERAL ENVIRONMENTAL IMPACT OF DIAGNOSTIC AND THERAPEUTIC MOLECULAR IMAGING PRODUCTION

Radioactive waste from medical isotopes inevitably arises during production, and their use and the amount of waste generated varies widely among different jurisdictions. Waste has to be stored or treated properly and according to local guidelines, considering the entire sequence of waste management operations.

For example, ^{99}Mo, the precursor of ^{99m}Tc, is produced in reactors, mainly in the fission process of ^{235}U (*3*). ^{99}Tc, the decay product of ^{99m}Tc, has a long half-life (211,000 y) and strong environmental mobility (highly soluble in the form of pertechnetate). Experiences—that is, from the Hanford Nuclear Plant—have highlighted the importance of environmental policies (*4*). On the basis of these experiences, the issue of ^{177m}Lu was solved using exclusively non–carrier-added ^{177}Lu, and the use of ^{225}Ac will soon be based on ^{225}Ac noncontaminated with ^{227}Ac. For instance, it is now estimated that at the time of injection, the accelerator-produced ^{225}Ac would contain 0.7% ^{227}Ac, which, although it can be considered negligible in the short term, has a long-term bioaccumulation (with a half-life of ∼22 y) that may not be entirely neglectable (*5*).

Furthermore, when finding and extracting raw material resources, apart from consumption of significant amounts of energy, less visible effects such as soil erosion and water pollution may occur (*6*). The production of radioactive isotopes also involves nuclear reactors or particle accelerators, which can contribute to significant energy consumption. This energy still likely comes mainly from fossil fuels (depending on the location or jurisdiction), contributing to greenhouse gas (GHG) emissions. However, whereas the energy cost of, let us say, ^{177}Lu at a research reactor might be substantial and also vary on the basis of differing age and design, with the entry of isotope production in power reactors the incremental energy cost for isotope production versus powering the reactor for energy production is now manyfold less.

Energy consumption is not limited to the production stage but also involves further downstream steps, that is, transportation.

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Thus, efficient on-site or local production can significantly reduce transportation's carbon footprint. Additionally, there is always a theoretic risk of spills or leaks, which can lead to environmental contamination beyond the estimated nuclear waste.

Lastly, imaging scanners also contribute to energy and resource consumption—during their manufacturing as well as during their actual use in daily clinical routine. Therefore, a modern production (and refurbishment and recycling) process with the least possible energy consumption while using recyclable materials and an environmentally conscious design is desirable.

ENVIRONMENTAL IMPACT OF HOSPITAL-BASED MOLECULAR IMAGING DEPARTMENTS

It is difficult to precisely quantify the contribution of nuclear medicine to the global environmental impact of health care. The overall health care carbon footprint contributes an average of approximately 5% of the national CO_2 footprint (Fig. 1) (*7*). Estimates for 2014 range from 3.5% in India to 7.9% in the United States and 8.1% in The Netherlands (*7*). Hospital care is the top contributor, with 36% of GHG emissions. These are U.S. data from 2013, when the relative contribution of health care to GHG emissions was estimated at 9.8% of the national total (*8*). The actual contribution of nuclear medicine is not known, but medical imaging (mostly from radiography, CT, and MRI, not including SPECT and PET) might contribute to up to 10% of the health care footprint, accounting for up to 1% of global GHG emissions (*9,10*).

It was calculated that a single large radiology department could emit GHG emissions equivalent to more than 400 single-family homes annually (*11*). In particular, Marwick et al. found certain MRI examinations to be responsible for the highest contribution. SPECT had 4%–11% of the contribution of MRI, and ultrasound had 0.5%–2% (*12*). Other estimates trend toward a similar gradient, with, for instance, 0.5 kg/study for ultrasound, 9.2 kg/study for CT, and 17.5–399.8 kg/study for MRI (*13,14*). Unfortunately, no such data are available regarding PET and modern cadmium-zinc-telluride–based SPECT devices.

On the basis of the abovementioned values and being careful not to consider those estimates as undisputed truths but rather as food for thought, one may envision several ways to reduce nuclear medicine's carbon footprint.

Use More Environment-Friendly Techniques to Diagnose Patients

When acceptable, transitioning to other techniques, that is, non–GHG-emitting examinations such as blood tests (which partly still need to be developed), could potentially enable initiation of treatment. As an example, when a patient with a chronic cardiac ischemic condition is triaged, a complete history and physical examination with an abnormal electrocardiogram and elevated cardiac enzymes can often guide patient management without the need for perfusion imaging. In another currently well-established example, most patients with a history of differentiated thyroid cancer are monitored using serum thyroglobulin without a need for periodic radioiodine scans or CT for their surveillance follow-up (*15*).

Do More Nuclear Medicine Studies

Increasing the ratio of (adequate) nuclear medicine techniques—for instance, instead of MRI—saves GHG emissions. Obviously, this is a somewhat oversimplistic view since many clinical indications are specific to MRI. Additionally, the generalization of hybrid imaging, that is, SPECT/CT and PET/CT, partly mitigates the benefit due to the higher footprint of CT, especially when underused.

Increase the Use of PET and SPECT Devices

Going from 8 to 12 scans per workday could decrease the environmental impact of SPECT by approximately 66% (*12*). This stems from the impact generated by assembly, transport, end of life, and, more importantly, stand-by electricity such as that consumed during nonoperational hours. Additionally, technologies such as full-ring cadmium-zinc-telluride (for SPECT) and silicon photomultipliers, and scanners with a long axial field of view (for PET), are much faster, allowing an increased use rate. This also includes artificial intelligence–based methods to denoise the images and provide equivalent diagnostic quality with significantly shorter acquisition times or lower injected doses (*16*). This partly allows older systems to be used longer and may have secondary positive consequences in terms of production, transport, and waste management.

Foster Frugal Innovation (Maybe Even Outside Nuclear Medicine)

Essential health care services are available to a maximum of half the world's population (*17*). Frugal innovation fosters the development of "low-cost and efficacious, new or adapted products (or services), mostly emerging from contexts of institutional voids and resource constraints, involving the creative use of existing resources" (*17*). The main benefit is the trickling-up effect, or reverse innovation—that is, innovations initially developed toward low- and moderate-income countries felt efficient enough to be used in high-income countries at a lower cost. Examples exist in radiology, notably in the development of U.S. devices (*18*).

Another hospital-based aspect again relates to waste management. It is estimated to be responsible for approximately 3% of the total health care carbon footprint (*19*). Therapeutic radioisotopes such as ^{131}I, ^{177}Lu, and ^{90}Y have longer half-lives, and subsequently, waste management becomes complex. Nuclear medicine departments that are treating inpatients have to deal with contaminated body fluids, the injection material, disposable clothing, plastic films that cover part of the hospital room, etc., and possibly even food. This waste may require storage for extended periods, often in low-temperature rooms, and hence, radiation protection requirements may contradict sustainability efforts. Countries that allow outpatient therapies with the current or upcoming modern radiotheranostic agents (i.e., ^{177}Lu-PSMA) are therefore balancing radiation protection and cost with the secondary benefit (probably beyond the original goal) of promoting sustainability in the practice of nuclear medicine. Also, the next generation of radiotheranostics may be partly geared more toward ^{212}Pb or ^{211}At, which have short half-lives.

Hospital heating, ventilation, and air conditioning systems generate the highest consumption of energy and CO_2 emissions (*20*). Considering that SPECT and PET devices, as well as the

NOTEWORTHY

- The main overall environmental impact in the future will come from Nuclear Medicine Therapies rather than diagnostic procedures.
- Potential negative impacts are, however, uncertain and need future decision tree sensitivity analysis.
- Several solutions are presented in this discussion, such as usage of radionuclides with shorter half-lives, increased usage of existing equipment, or balancing production versus transportation, among others.

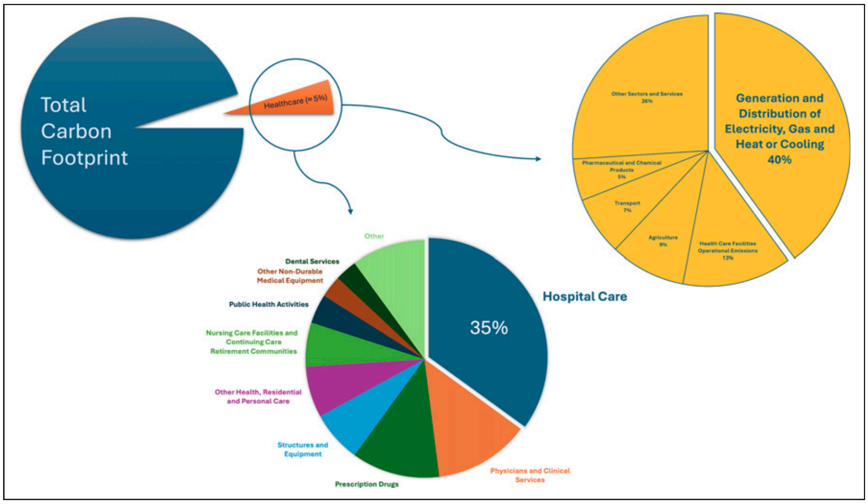

FIGURE 1. The healthcare system contributes to approximately 5% of total carbon footprint worldwide. In terms of the most responsible activity for GHG production, "generation and distribution of electricity, gas and heat or cooling" has highest share (~40%). Regarding the most responsible sector, "hospital care" contributes to more than one third of health care footprint.

abovementioned waste storage rooms, are required to be maintained at specific cool temperatures, smart heating and cooling systems (available already for home use) can support the sustainability efforts. Vendors will need to develop energy-saving states in which the imaging system can remain when not in use without impacting the required temperature.

Also, turning off workstations after core working hours could reduce total energy consumption by approximately one third, resulting in an extrapolated saving of more than 22 tons in CO_2 emissions per year in a single-center experience (*21,22*). Lastly, using highly efficient lighting and energy-friendly bulbs (e.g., motion-detector lights) in the department can create significant annual energy savings.

WHAT ARE THE OUT-OF-HOSPITAL SOLUTIONS?

Reducing the Environmental Impact of the Increasing Use

It is expected that the large number of patients on whom radiopharmaceuticals are used will grow. If addressing only 5% of cancer patients (global prevalence of 44 million (*23*)), this would mean that more than 8 million doses of radiopharmaceuticals will have to be produced yearly. Thus, increased radioactive waste will have to be taken care of, but additionally, the amount of radioactivity to be released in water 10 y from now, without protective measures, will be substantial. With long-half-life radionuclides such as ^{177}Lu (6.7 d) and ^{225}Ac (9.9 d), the water contamination may reach a level that raises serious concerns. In some U.S. centers, patients are requested to wear diapers during the first days at home and to keep them in a safe container until full decay (respectively, 2 and 3 mo). Thus again, shorter-half-life radionuclides without long-half-life contaminants may have a competitive advantage in this scenario.

^{225}Ac- and ^{177}Lu-labeled drugs appear to be on their way to becoming the future blockbusters of nuclear medicine and possibly will generate significant revenues for the industry during the next 15 y. Although currently in development with somewhat uncertain market and distribution uptake, an equivalent efficient drug labeled with a shorter-half-life radionuclide, such as ^{211}At or ^{212}Pb, has, however, a great chance to claim a significant market share over the long term, if showing at least equal efficacy.

Reducing the Impact of Transport and Travel

When considering radionuclides with shorter half-lives, the number of production sites needs to be increased, and the balance between investment in new sites and transportation costs must be evaluated carefully. However, the example of the production of ^{18}F (900 cyclotrons among the 1,500 operating cyclotrons in the world in good-manufacturing-practice condition (*24*)) shows that the industry is actually able to develop large networks of production tools. Although this corresponded to over 25 y and a $4 billion investment, a network of about 30 ^{211}At production units that could easily cover the 3 major markets would correspond to not more than a $600 million investment, less than what is now spent to develop the ^{225}Ac production network and far above what will be required to achieve worldwide access to ^{212}Pb.

Lastly, providing remote access, such as through telereporting, can help reduce the carbon footprint by decreasing pollution and energy use related to transportation. This is also implied in research programs and scientific events. If open-access cloud-based databases become available for radiopharmaceutical purposes, they will obviously decrease the need for the same research studies to be initiated in other jurisdictions. International scientific events can have a significant carbon footprint, which should be considered. It was calculated that attending the Radiological Society of North American annual meeting generates a carbon footprint equal to the average annual footprint of 3,689 people living in high-income countries, 10,560 people living in middle-income countries, or 123,072 people living in low-income countries (*25*).

Using the Current Long-Half-Life Therapeutics Equitably

Although long-half-life therapeutics can be more impactful on the environment, some measures can be taken to limit their adverse effects. For example, adapted radionuclide therapy, instead of a fixed-dosing approach, will help to optimize dosage and radiopharmaceutical waste. Dosimetry can maximize the benefit-to-risk ratio for patients by calculating the maximum tolerated activity in a personalized manner. SPECT serves as the primary posttreatment quantification modality for dosimetry, and with current cadmium-zinc-telluride technology and artificial intelligence–based image reconstruction techniques, scanning time can be reduced and multiple sessions of dosimetry after therapy can be omitted (*26*). Also, there are novel artificial intelligence–based methods, such as digital twins, that can provide a precise virtual analog of each individual patient before administration of radiopharmaceutical therapy (*27*).

CONCLUSION

The growth in diagnostic and therapeutic radiopharmaceuticals is based on an increasing number of new molecules and new indications and an expansion of clinical applications. We have discussed the impact of this growth on various levels, such as in terms of life expectancy (which such new therapies are actually trying to increase), social issues such as ambulatory (with impact on home care) versus inpatient care. However, it is only with a true decision tree sensitivity analysis that these potential negative effects can be evaluated. Only then can solid outcomes be generated from what-if scenarios. We cannot currently say what the environmental impact would be if survival were shortened by doing suboptimal or fewer tests, if earlier interventions were not possible because of testing restrictions, and if there were downstream effects from a significant rise in health care costs.

Although potentially controversial, we have shown scenarios in which nuclear medicine procedures can provide alternatives for other, potentially more detrimental, imaging modalities. We hope that the points we have raised and the demonstrated scenarios may serve as a basis for further discussion about the little-known environmental impact of nuclear medicine and radiotheranostics.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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