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PAPER

Development of the occupational exposure during the production and application of radiopharmaceuticals in Germany

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Abstract

An increasing number of radiopharmaceuticals and proteins are available for diagnosing and treating various diseases. The demand for existing and newly developed pharmaceutical radionuclides and proteins is steadily increasing. The radiation exposure levels of workers in the radiopharmaceutical industry and nuclear medicine field are closely monitored, specifically their effective dose and equivalent dose, leading to the question, of whether the dawn of radiopharmaceuticals affects the occupational exposure level. This development is analyzed and evaluated with data from the German National Dose Register. Data shows that the effective dose in the work categories production and distribution of radioisotopes as well as nuclear medicine slightly decreased from 1997 to 2021. Over the same period, the hand equivalent dose in nuclear medicine increases steadily, with no discernible trend in production and distribution of radioisotopes. Over the past few decades, intentional efforts and measures have been taken to ensure radiation protection. Instruments for monitoring and dose reduction must be continuously applied. Given the low effective dose, the focus in future shall be on dose reduction following the as low as reasonably achievable principle. The development of the hand equivalent dose should be carefully observed in the upcoming years.

1. Introduction

Over the past few decades, pharmaceutical radionuclides and specially developed proteins have gained attention for their role in diagnosing and treating various diseases and metabolic conditions. These substances are used to diagnose and treat conditions such as tumours, metastases, dementia, and heart disease. The need for pharmaceutical radionuclides will grow strongly in the coming decades (Ligtvoet *et al* 2021, Arnold 2022, pp 58, 59, Mantel and Williams 2019).

Diagnostics focus on the following radionuclides: ^{11}C, ^{18}F, ^{68}Ga, ^{89}Zr, ^{99m}Tc, ^{111}In and ^{123}I. Despite new upcoming radionuclides, ^{99m}Tc accounts for around 70% of all nuclear medicine applications for diagnostics (IAEA 2010b, p 14). While in molecular radiotherapy, the focus is particularly on ^{90}Y, ^{131}I, ^{149}Tb, ^{153}Sm, ^{166}Ho, ^{177}Lu, ^{223}Ra, ^{225}Ac, and ^{227}Th (Cutler 2019, Mantel and Williams 2019, Radchenko *et al* 2021, Strahlenschutzkommission 2022). Alpha emitters are of explicit interest due to their shorter path ranges and high linear energy transfer. The primary clinical use is focused on ^{223}Ra, while clinical trials are primarily conducted on ^{225}Ac and ^{227}Th. Meanwhile, ligands linked to ^{212}Bi, ^{213}Bi, ^{212}Pb, and ^{211}At are currently under trial too (Pallares and Abergel 2022, Zhang *et al* 2023). Additionally, research and application intensively handle radionuclides that enable the production of a radionuclide generator. These are radionuclide pairs, e.g. ^{68}Ge/^{68}Ga, ^{82}Sr/^{82}Rb, ^{90}Sr/^{90}Y and ^{188}W/^{188}Re (IAEA 2010a, pp 5, 6). At the moment, the research community already look into optimizing procedures: preclinical trials investigate whether substituting radionuclides with similar properties induces an increased serum stability, higher uptake into target tissues, more efficient energy transfer or optimized imaging quality (Radzina *et al* 2023, pp 29–32). Research on theragnostic radionuclides (e.g. ^{64}Cu & ^{67}Cu, ^{44}Sc & ^{47}Sc, ^{86}Y & ^{90}Y, ^{83}Sr & ^{89}Sr) is also highly interesting due to the possibility of performing diagnostics and therapy simultaneously with the same radionuclide or different radionuclides with same or similar chemical properties (IAEA 2021, p 2, Miller *et al* 2022). Currently, theragnostic radionuclides are already used in diagnostics and therapy as a considerable contribution to personalized medicine. For diagnostics and therapy ^{123}I & ^{131}I, ^{68}Ga & ^{177}Lu, ^{68}Ga & ^{90}Y, ^{18}F & ^{131}I are used, respectively (Yordanova *et al* 2017). The majority of the aforementioned radionuclides are already used in regular clinical practices and not only in preclinical studies (Radzina *et al* 2023, p 39).

Radiopharmaceuticals and protein vectors and their application become increasingly popular and have expanded rapidly in the recent decade. The demand for various proteins and their labeled or carrier-free radionuclides in diagnostics and therapy continues while many obstacles lay ahead: new production methods, improving labeling chemistry and new oncologic targets combined with new targeting tissue vectors. (Flux *et al* 2017, Roesch and Martin 2023)

With programmes like PRISMAP (The European medical isotope programme: production of high purity isotopes by mass separation) or National Isotope Development Center previously hard-to-reach and underutilized radionuclides are now easier to access. Those programmes offer a supply chain for radionuclides produced by newly set-up institutions like CERN-MEDICIS (CERN-MEDical Isotopes Collected from ISOLDE) and already well-known institutions like POLATOM. (Duchemin *et al* 2021, 2020, Radzina *et al* 2023, p 28, Radzina *et al* 2022)

Dosimetric monitoring has been heavily researched and optimized for the past two decades. The main goals are finding practical methods for reducing the effective dose and equivalent dose as well as strengthening the knowledge of handling procedures with significantly high exposures. Recently Baudin *et al* (2023), Alashban and Shubayr (2021) and Villoing *et al* (2018) presented a trend review of occupational exposure in nuclear medicine in France, Saudi Arabia and the USA. Vogt (2022) created an inspection manual for the implementation of practical measures for dose and risk reduction. Donzé *et al* (2022) developed an audit tool for checking the application process of radiopharmaceuticals in nuclear medicine. Furthermore, several researchers including McCann *et al* (2023), Andriulevičiūtė *et al* (2022), Riveira-Martin *et al* (2022), Aalbersberg *et al* (2021), Thakral *et al* (2018), Salesses *et al* (2016), Carnicer *et al* (2011), Rimpler *et al* (2011), Sandouqa *et al* (2011), as well as Rimpler and Barth (2007) conducted studies on nuclide-specific research for exposure situations, accurate dosimetric monitoring and optimizing the exposure situation for the application of radiopharmaceuticals in nuclear medicine. Wrzesień (2018), Biegała and Jakubowska (2020) as well as Balbona and Guevara (2016) reported about such aspects specifically for the production of radiopharmaceuticals. Transitioning such research efforts into generally applicable recommendations Bundesamt für Strahlenschutz Germany published various guidelines for a variety of procedures and radionuclides - e.g.:Bundesamt für Strahlenschutz 2009, 2013a, 2013b, 2015a, 2015b, 2017.

At the moment, no detailed, all-encompassing systematic review presents the exposure situation of workers in production and application of radiopharmaceuticals in Germany. UNSCEAR (2022) represents a systematic, worldwide review and evaluates occupational exposure in many fields. In this report, nuclear medicine and radioisotope production and distribution are separately presented (UNSCEAR 2022, pp 110, 111, UNSCEAR 2022, pp 92–97).

A rising number of handled activity and radionuclides could principally lead to a changing exposure situation and subsequently to a different pattern and level of radiation dose received by workers. The German National Dose Register (Strahlenschutzregister—SSR) at Bundesamt für Strahlenschutz, functioning as the National Dose Register, records, monitors and evaluates the corresponding occupational dose data in Germany for all personnel. The legal basis of the SSR is derived from the Radiation Protection Act (§ 170) and the Radiation Protection Ordinance (§ 173), implementing the European Radiation Protection Directive 2013/59 Euratom. Data collection aims to monitor compliance with the legal dose limits and radiation protection principles. Furthermore, the recorded dose data serve to verify the existence of a claim against statutory accident insurance and for scientific research purposes.

Since the continuously growing database of the SSR is of scientific importance, it is also made available to epidemiological research in anonymized form. Thus, one of the tasks of the SSR is to make the dose data available for scientific research upon request. The SSR contributes to further developing occupational radiation protection according to the state of the art in science and technology.

Presuming an increase in the total handled activity and radionuclides the exposure level in radionuclide laboratories may change to a higher level. This raises the question, of whether the increasing demand and use of radiopharmaceuticals affects the occupational exposure level in fact and whether it can be proven with the data registered at SSR.

2. Method

The SSR summarizes dose determinations from different dosimetry monitoring service in Germany. The occupational life effective dose is summed up from many individual values over the time of occupational practice (Frasch 2005, pp 25, 26). The evaluations which are presented in this work are based on the state of the SSR database on 1 July 2022.

In this context, it is important to mention, that the central collection of dose data started in 1997 for the measurement of personal dose equivalent and in 2002 for the committed effective dose. Data from monitoring under the responsibility of the German Democratic Republic were also integrated. However, data that had already been collected previously and that were available digitally at the dosimetry services or could be digitized were also transferred to the SSR retrospectively. Thus, the database in the SSR reaches back to the 1960s, whereby the data in the earlier monitoring periods are only incompletely available. (Vogt 2022, p 79)

According to § 170 par 1 Radiation Protection Act, data from the SSR is accessible for research purposes in an anonymized form. Considering the aforementioned aspects the shared dataset from the SSR was analyzed and evaluated from 1997 until 2021. The database does not allow an activity-related detailing of the dose distribution for different professions as presented by Chruscielewski *et al* (2002) or Martins *et al* (2007).

In this work, data for the effective dose and equivalent dose of the hand and eye lens are presented. These data are derived from measurements with specific dosimeters calibrated for the personal dose equivalent $H_P(10)$, $H_P(0.07)$ and $H_P(3)$ as well as dose determination of incorporated radionuclides. The measured values for $H_P(10)$ are reported to the SSR with a measurement uncertainty ($k = 1$) of 0.1 mSv, those for $H_P(0.07)$ with 1 mSv. For measured values below 0.05 mSv for $H_P(10)$ or 0.5 mSv for $H_P(0.07)$, the dose value is set to 0.0 mSv. A separate rounding rule applies to the measurement of $H_P(3)$. The measured values are reported with a measurement uncertainty of 0.1 mSv, whereby the lower reporting threshold is 0.25 mSv.

The SSR collects data from internal and external exposures. Each dose determination is linked to a year. Therefore one can analyze data for each calendar year separately and compare the dose data with regulatory dose limits. When exceedances of regulatory dose limits occur, the German federal competent authories typically impose further measures and optimization within the handling process. Principally a competent authority can allow an effective dose of up to 50 mSv for one calendar and up to 100 mSv over five years (§ 78 par 1 Radiation Protection Act).

Each occupationally exposed person is registered with a so-called work category, which describes the activity and occupation. The scope of this research includes data from the work category production and distribution of radioisotopes as well as nuclear medicine.

Work categories were updated in 2018 with additional ones included. Until 2018 the work category 'others' existed. Workers could had been registered in 'others' until 2018, but now have been assigned to the 'correct' work category.

The work category production and distribution of radioisotopes include the operations (Bundesamt für Strahlenschutz 2018)

- production and transport of radiochemical pharmaceuticals, radioactively labeled compounds, tracers for nuclear medicine, research, or industry,
- production and transport of industrial sources for non-destructive testing or for measuring probes,
- and operation of cyclotrons for radionuclide production.

This work category combines the production and transport of sealed and unsealed radioactive substances. Therefore, one cannot aim for a dataset only for the production of pharmaceutical radionuclides.

The work category nuclear medicine scopes the following activities (Bundesamt für Strahlenschutz 2018)

- application of radiopharmaceuticals in imaging procedures,
- and therapy with open radioactive substances.

A distinction is made between monitored and measurably exposed persons: The number of monitored persons includes all persons for whom entries are available in the register. The number of measurably exposed persons describes all persons with a dose value greater than 0 mSv. The exposure situation of monitored persons with a dose of 0 mSv was either successfully optimized or monitoring took place but no exposure existed. These can be persons such as e.g. IT employees or product managers. (Vogt 2022, pp 80, 81) In the medical field, the aspect of '(measurably) not exposed' personnel was described by Rosentreter and Oeh (2018, p 3).

In this research, the data of the measurably exposed persons are considered for analyzing the mean, median and maximum doses. While looking into dose distributions all monitored persons are taken into

Table 1. Number of monitored persons from 1997 to 2021 in total listed in SSR for different dose types.

Work category/dose type	Effective dose	Hand equivalent dose	Eye lens equivalent dose
Production and distribution of radioisotopes	91 390	8 421	89
Nuclear medicine	251 808	81 651	168

Table 2. Number of measurably exposed persons from 1997 to 2021 in total listed in SSR for different dose types.

Work category/dose type	Effective dose	Hand equivalent dose	Eye lens equivalent dose
Production and distribution of radioisotopes	14 287	1 348	31
Nuclear medicine	113 030	44 179	68

account. This research includes a varying number of monitored persons and measurably exposed persons. Tables 1 and 2 provide, respectively, a breakdown of the number of monitored persons and measurably exposed persons from 1997 to 2021.

Frasch (2005, p 27) emphasizes that the quality of the evaluation strongly depends on the completeness of the data. For the trend analysis, the correct knowledge of the work category is of crucial importance. The analysis and evaluation within the scope are based on the confidence that the licensees register their occupationally exposed persons within the correct work categories.

3. Results

3.1. Progression of effective dose

Figure 1 displays the mean, median and maximum values of the effective dose per calendar year. It shall be taken into account that the effective dose is the sum of the committed effective dose for internal exposure and the personal dose equivalent $H_P(10)$ for external exposure.

From 1997 to 2021 the number of measurably exposed persons ranged from 316 to 886 persons per year in production and distribution of radioisotopes and from 1594 to 5710 persons per year in nuclear medicine for the effective dose.

In the work category production and distribution of radioisotopes, the mean effective dose decreases from the year 1997 (3.9 mSv) to the year 2002 (0.7 mSv). Between the years 2002 and 2021, the mean effective dose varies from 0.6 mSv in 2020 to 1.3 mSv in 2009. In the work category nuclear medicine, the mean effective dose decreases from the year 1997 (1.4 mSv) to the year 2003 (1.0 mSv). Between the years 2003 and 2021, the mean effective dose varies between 0.6 mSv in 2015 and 1.0 mSv in 2003 without significant changes. It can be observed that the mean effective dose decreased by a factor of 6 from 1997 to 2002 in production and distribution of radioisotopes and by a factor of 1.4 in nuclear medicine.

From 2002 to 2021 a slight but discernible reduction of the mean effective dose is evident for nuclear medicine. From 2002 to 2021, the mean effective dose changed from 1. 04 mSv to 0.75 mSv ($R^2 = 0.836$). For nuclear medicine, this trend is also confirmed by Bundesamt für Strahlenschutz (2022, p 53). For production and distribution of radioisotopes the mean effective dose reduced too, but varies more than in nuclear medicine between 0.61 mSv to 1.33 mSv ($R^2 = 0.018$).

For the work categories nuclear medicine and production and distribution of radioisotopes, the median effective dose decreased from 1997 to 2021 steadily, while peaking at 0.8 mSv and 1.0 mSv respectively.

The maximum values of the effective dose per calendar year in the work category production and distribution of radioisotopes vary between 74.8 mSv in 1998 and 5.6 mSv in 2021. The maximum values of the effective dose per calendar year in nuclear medicine differ between 9.0 mSv in 2017 and 30.5 mSv in 2020.

As reported in figure 1, the median effective dose is constantly lower than the mean effective dose in both work categories. This argues for a left shift in the dose distribution towards more abundant dose registrations in low-dose intervals. Additionally, it can be shown, that in nuclear medicine as well as production and distribution of radioisotopes for some individuals the regulatory limit for the effective dose (20 mSv) is exceeded. Figure 1 only presents the maximum effective dose registrations per calendar year. However, even more persons may received a total effective dose per calendar year higher than the regulatory dose limit. However, these can only be identified via the dose distributions.

3.2. Comparison of internal and external exposure

In both work categories external exposure is responsible for over 99% of the total effective dose. An analysis of the committed effective dose is not expedient, since few measurably exposed persons are registered in both work categories.

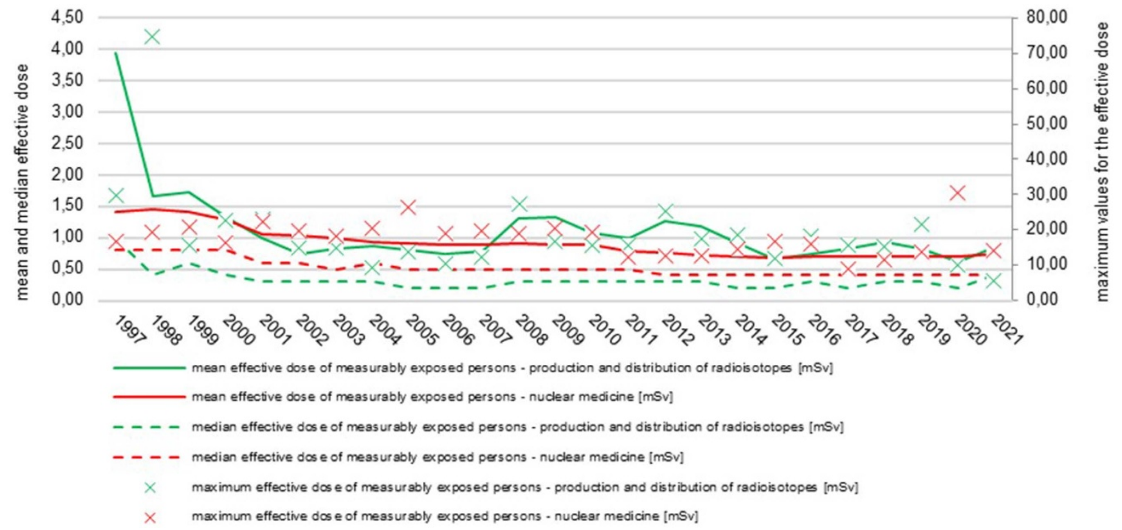

Figure 1. Development of the mean, median (left axis) and maximum values of the effective dose (right axis) of the work categories 'nuclear medicine' and 'production and distribution of radioisotopes' per calendar year in Germany.

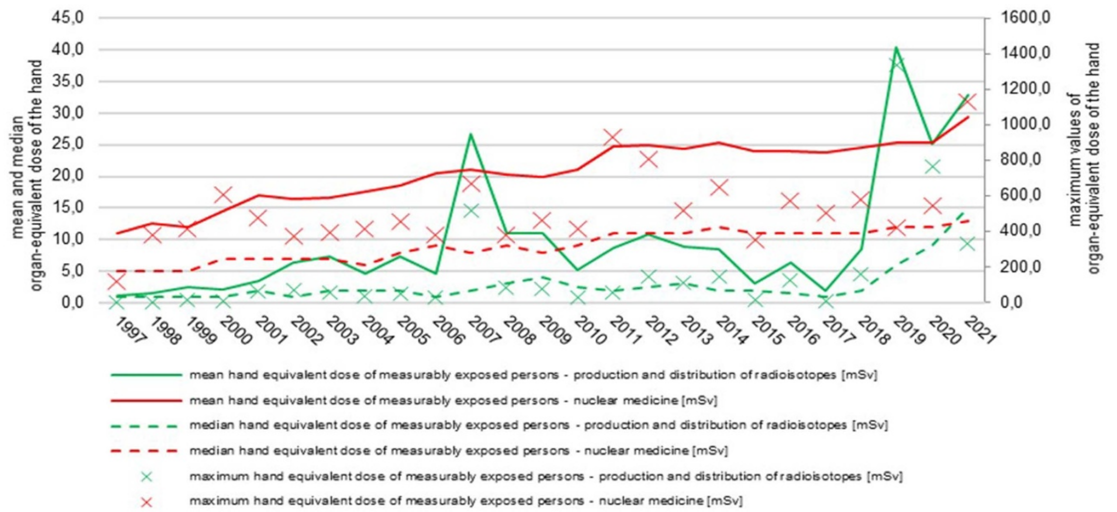

Figure 2. Development of the mean, median (left axis) and maximum values of the hand equivalent dose (right axis) of the work categories 'nuclear medicine' and 'production and distribution of radioisotopes' per calendar year in Germany.

Why mainly external exposures are registered can only be assumed: the responsible radiation protection supervisors implement protective measures before handling radioactive substances, with the aim that no permanent incorporation monitoring according to the German guideline for the physical radiation protection control for determination of the body doses-incorporation monitoring (RiPhyKo-part 2) becomes necessary. (Vogt 2022, p 88)

Reaching this goal, the work activity, handling time, handling frequency or handling location, e.g. activities in fume hoods, glove boxes or process cells, is optimized by licensees intentionally. A very low share by internal exposure is shown by Noh *et al* (2023, p 375) as well. UNSCEAR (2022, pp 92, 110) confirms this sighting for both fields too. UNSCEAR (2022, pp 92, 110) emphasises, that the exposure level depends on the level of radiological protection measures applied in the workplace.

3.3. Progression of the hand equivalent dose

Figure 2 displays the mean, median and maximum values of the hand equivalent dose per calendar year.

From 1997 to 2021 the number of measurably exposed persons ranged from 15 to 318 persons per year in production and distribution of radioisotopes and from 496 to 2 791 persons per year in nuclear medicine for the hand equivalent dose.

In the work category production and distribution of radioisotopes, the mean hand equivalent dose varies from 1.2 mSv in 1997 to 40.5 mSv in 2021. From 1997 to 2018 the mean hand equivalent dose shows no significant increase. From 2018 onwards an increase is clearly visible. The mean hand equivalent dose in nuclear medicine increases steadily from the year 1997 with 11.1 mSv to the year 2021 with 29.5 mSv.

For the mean hand equivalent dose in the work category production and distribution of radioisotopes no distinct and discernible trend can been seen. Hence during this period, the mean hand equivalent dose rises by threefold in nuclear medicine.

In the work category nuclear medicine, the median hand equivalent dose steadily increases from the year 1997 (5 mSv) to 2021 (13 mSv). The same development is evident in the work category production and distribution of radioisotopes: the median hand equivalent dose constantly rises from the year 1997 (1 mSv) to 2021 (15 mSv).

The maximum values of the hand equivalent dose in the production and distribution of radioisotopes vary between 4 mSv in 1997 and 1998 and 162 mSv in 2018. In 2007, 2019, and 2020, there are outliers in the maximum values, respectively, 516 mSv, 1 335 mSv, and 769 mSv. The maximum hand equivalent doses in nuclear medicine differ between 121 mSv in 1997 and 670 mSv in 2007. In 2011, 2012, and 2021, there are outliers in the maximum values with, respectively, 933 mSv, 809 mSv, and 1 130 mSv.

As seen in figure 2, the median hand equivalent dose consistently appears lower than the mean hand equivalent dose in both work categories. The dose distribution for the hand equivalent dose can be characterized similar to that of the effective dose: a noticeable left-shift for low-dose intervals.

Based on the data, there is a noticeable contrast between the two work categories. Specifically, nuclear medicine consistently exhibits higher maximum values than the production and distribution of radioisotopes. Figure 2 only presents the maximum hand equivalent dose registrations per calendar year. However, even more persons may received a total hand equivalent dose per calendar year higher than the regulatory dose limit. However, these can only be identified via the dose distributions.

3.4. Progression of the eye lens equivalent dose

Before lowering the regulatory equivalent dose limit for the eye lens from 150 mSv to 20 mSv per calendar year in 2018, the measurand personal dose equivalent $H_P(0.07)$ was used usually for dose determinations. This was possible as an approximation since the measurand personal dose equivalent $H_P(0.07)$ for monitoring eye lens equivalent dose is suitable for all pure photon radiation fields without a significant proportion of beta emissions (Behrens *et al* 2017, pp 6, 11). However, with the implementation of the new regulatory dose limit, the measurement parameter personal dose equivalent $H_P(3)$ was introduced as a measurement quantity for the eye lens equivalent dose with § 171 Radiation Protection Ordinance in conjunction with Annex 18 Part A Radiation Protection Ordinance in 2018. With lowering the dose limit for the eye lens equivalent in 2018 licensees had to monitor the eye lens dose. Before the necessity to monitor the eye lens exposure was barely seen by licensees.

Therefore, the dataset for the eye lens equivalent dose is rather small compared with other dose figures. In 2021 only a few handful of measurably exposed persons are registered in the work categories nuclear medicine as well as production and distrbution of radioisotopes: respectively 22 and 30. This dataset does not allow any generalizing statements on the development of the eye lens equivalent dose, so the data are not presented further here.

3.5. Dose distribution of the effective dose and hand equivalent dose

Understanding the distribution of doses when handling radiopharmaceuticals is crucial in determining the extent of exposure to occupationally exposed individuals. This information can help identify those who may have been overexposed as well as those who have been minimally exposed. Therefore, dose distributions from the year 2016–2021 are presented.

The relative proportions of each dose interval presented in figures 3–6 were calculated from the absolute number of monitored persons of the dose interval and the total number of monitored persons of each calendar year per work category.

Figure 3 displays the dose distribution of the effective dose in production and distribution of radioisotopes. From 2016 to 2020, it can be seen that in the dose interval of 0.0 mSv steadily fewer individuals are recorded. The proportion decreased from 88% to 70%. In 2021, the proportion for the dose interval of 0.0 mSv was 62%. The proportion of people in the dose interval >0–0.5 mSv increases from the year 2016 with 8% to the year 2021 with 20%. Furthermore, for dose intervals >0.5 mSv, the proportion is relatively low, ranging from 3.6% to 16.5% across all years.

Figure 4 represents the dose distribution of the hand equivalent dose in production and distribution of radioisotopes. There has been a significant decrease in the dose interval of 0.0 mSv, which has gone from 88% to 41% between 2016 and 2021. In the dose interval >0–1 mSv, the relative shares from 2016 to 2021

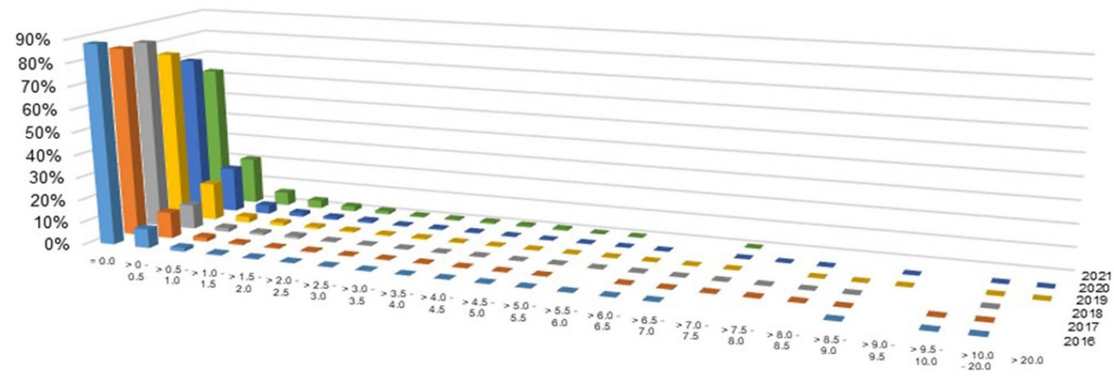

Figure 3. Dose distribution of the effective dose in production and distribution of radioisotopes from the year 2016–2021.

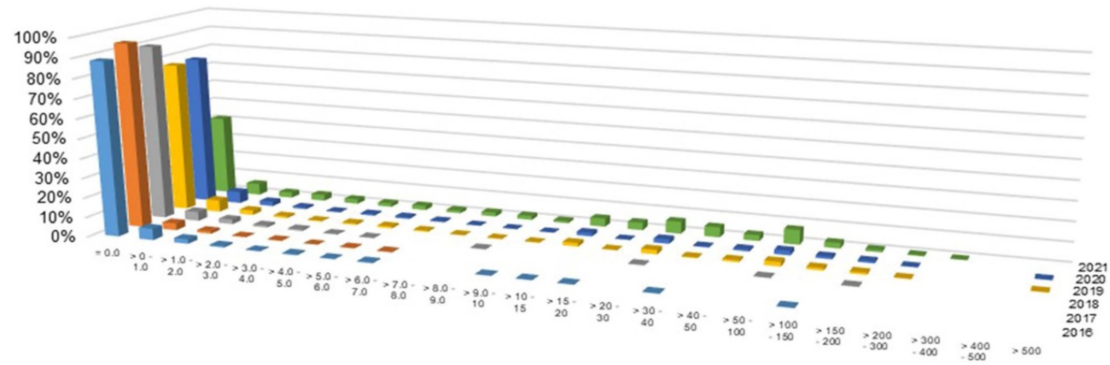

Figure 4. Dose distribution of the hand equivalent dose in production and distribution of radioisotopes from the year 2016–2021.

change between 3.5% and 6.1%. It can be seen that from 2016 to 2018, few or no dose values were registered in the dose intervals of >6 mSv. From 2019 to 2021, the relative share of dose reportings in the dose intervals of >6 mSv increased: in 2017, one person was registered with a hand equivalent dose >6 mSv and in 2021, 223 persons were registered. According to the database, the percentage of the hand equivalent dose >6 mSv increased from 0.25% in 2017 to 40.5% in 2021, indicating a rise in the occurrence of such doses.

Outlining the development of dose distribution of the effective dose and hand equivalent dose in production and distribution of radioisotopes shows a significant change in the relative shares. This change from the year 2018 onwards is probably due to the restructuring of the work categories. Previously, individuals were likely registered in other categories or in the work category 'others', which was abolished as part of the restructuring.

The categories were restructured due an old systematics, which was imprecise. Hence the work categories were adapted to the UNSCEAR systematics. Nowadays a more precise data analysis is possible, but some time series of work categories could show a break or an inconsistency.

Figure 5 displays the dose distribution of the effective dose in nuclear medicine. In the dose interval 0.0 mSv, the proportion varies between 53% and 58%. The proportion of the dose interval >0–0.5 mSv varies between 24% and 26% in all years. The relative share of the dose interval >0.5–1.0 mSv varies between 7% and 9% in all years. The percentage of the dose interval >1.0–1.5 mSv varies between 4% and 5% in all years. The proportion in dose intervals >1.5 mSv varies between 4% and 5% between 2016 and 2021.

Figure 6 depicts the dose distribution of the hand equivalent dose in nuclear medicine. The relative share in the dose interval 0.0 mSv varies between 43% and 45% in all years. The proportion of the dose interval >0–1 mSv varies between 6% and 7% in all years. The proportion of the dose interval >1–2 mSv and >2–10 mSv varies, respectively, from 3% to 4% and from 0.9% to 3.2% in all years.

Based on a graphical analysis it could be assumed that there is an increased proportion of individuals in the dose intervals for the hand equivalent dose in the nuclear medicine category between >10–100 mSv. However, since the dose intervals of >1–10 mSv are more finely disaggregated, this may lead to a fallacy. When analyzing the raw database, it can be observed that in the dose distribution in the dose intervals of >0–10 mSv, the same number of individuals were reported as in the dose intervals of >10–100 mSv.

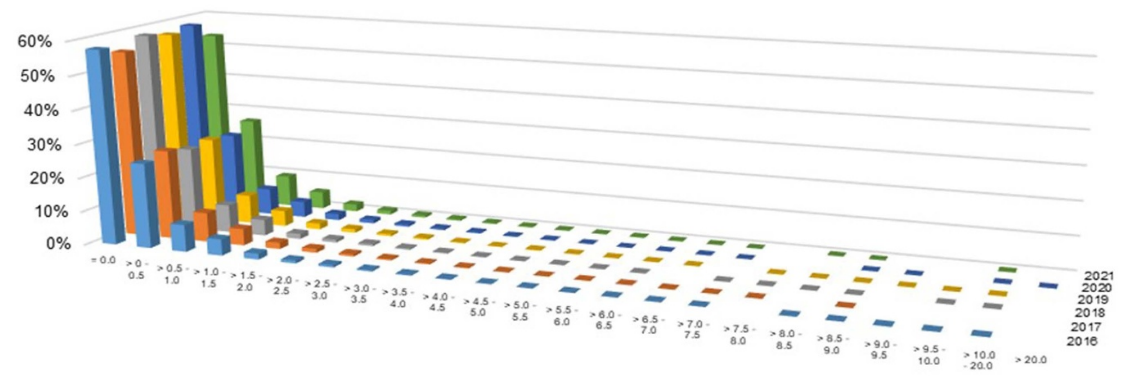

Figure 5. Dose distribution of the effective dose in nuclear medicine from the year 2016–2021.

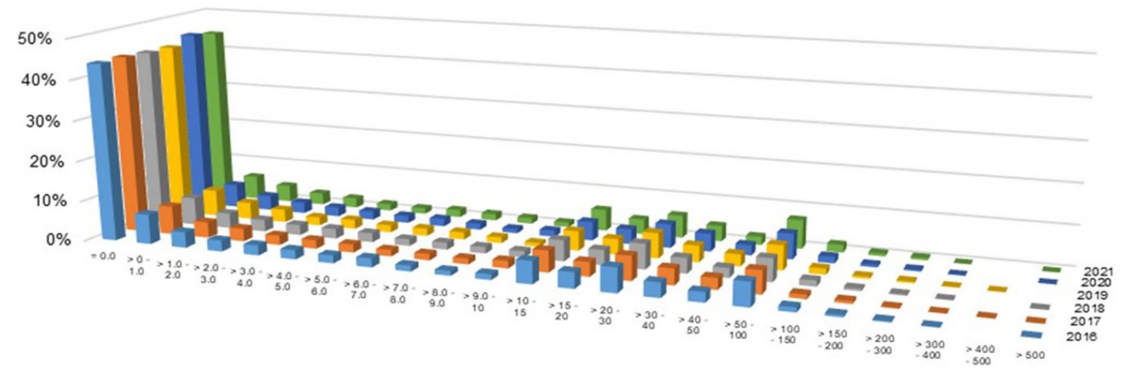

Figure 6. Dose distribution of the hand equivalent dose in nuclear medicine from the year 2016–2021.

When analyzing the raw database for dose distributions from year 2016 to 2021, in total there are slightly more exceedances of the regulatory dose limits for the work category nuclear medicine. Relatively seen to the number of monitored persons the percentage of exceedances of the regulatory dose limits is similar in both work categories.

4. Discussion

4.1. Main trends

It is evident that the mean and median effective dose in the area of production and application of pharmaceutical radionuclides, corresponding to the categories production and distribution of radioisotopes as well as nuclear medicine, is steadily decreasing. A decreasing trend in the mean effective dose representing the stochastic health risk displays an effort for optimizing protection in the pertinent exposure situations by radiation protection supervisors and workers. This effort leading to optimization is confirmed by Rosentreter and Oeh (2018, p 3).

There is currently no distinct and discernible trend in the development of the hand equivalent dose in production and distribution of radioisotopes. Following the restructured work categories in 2018, it can be assumed, that after a transition time, all occupationally exposed personnel are correctly registered in the SSR database. Another evaluation of the database may be needed. Meanwhile, this transition is not existent in nuclear medicine: a steady increase can be seen for the median and mean hand equivalent dose. This trend shall be watched carefully by the competent authorities, radiation protection supervisors and workers. This trend can be confirmed in nuclear medicine departments worldwide: UNSCEAR (2022, p 92) reports, that average hand equivalent dose have increased over time.

The causes of this trend shall be determined and possibilities for dose minimization shall be considered. Possible causes may be a lack of radiation safety culture in nuclear medicine (European Commission 2010, p 5) or an increasing handling activity and frequency in nuclear medicine. Due to the dawn of personalized medicine by radiopharmaceuticals, a higher handling activity can be foreshadowed. Higher handling activities and frequencies are prone to overexposures.

When analyzing the hand equivalent dose in production and distribution of radioisotopes from 1997 to 2021 in detail, one will recognize principally a smooth increase of mean hand equivalent dose (figure 2). In 2007 and 2019 two quite high maximum hand equivalent doses exist. In 2007 and 2019, the dataset with its dose distribution show just one high value in each year. Due to the fact how mean values are calculated one high value pushes the mean value tremendously up. Hence, it is important to analyze the median values too. The median hand equivalent doses in production and distribution of radioisotopes do not vary significantly between 1997 and 2018. Since 2018 however, a steady increase can be observed. The reasons for this development cannot be determined at the moment. Possible reasons can be the restructuring of the work categories or an actual increase of the mean and median hand equivalent dose.

The analysis of dataset from the work category production and distribution of radioisotopes joins the production and transport of sealed and unsealed radioactive substances. In reality, the exposure situations while handling sealed and unsealed substances may be similar for some radionuclides but can vary significantly. Incorporation risk increases while handling unsealed sources. Additionally, high-energy beta emitters designated for therapy (e.g. ^{90}Y and ^{177}Lu) and produced in radiopharmaceutical production companies demand a different shielding than sources for gauges, references and calibration purposes or x-ray fluorescence (e.g. ^{60}Co, ^{90}Sr, ^{137}Cs and ^{226}Ra). A separate analysis of the different working fields may be possible by introducing new work categories. With the introduction of new work categories, it could be differed between the production of radiopharmaceuticals regardless of the use in diagnostics or therapy and the production of industrial sources. The production of radiopharmaceuticals could be distinguished between the operation of cyclotrons and pure processing facilities. Sealed and unsealed sources are commonly transported in one vehicle and therefore should be summarized together as one work category. Additionally, the current dataset contains all registered doses for the work category production and distribution of radioisotopes regardless of the handled radionuclides. Hence, the data enquiry could be filtered by specific radionuclides, which are connected unambiguously to radiopharmaceutical production. A great concern is, that still some radionuclides are not only used as radiopharmaceuticals but as well for industrial purposes in a sealed or unsealed form. This uncertainty can only be minimized by looking into the dose data from each licensee, which is not possible due to the anonymized form of the dataset.

The analysis of the distribution of the maximum dose registrations per calendar year per work category illustrates that in nuclear medicine more exceedances of the regulatory limits per individual dose registration occur than in production and distribution of radioisotopes. This evaluation of individual dose registrations shows, that in nuclear medicine higher individual doses are induced. However, this analysis cannot be used for a general statement on the situation of regulatory dose limit exceedances. Therefore, one needs to analyse dose distributions. In this regard it is important to acknowledge, that relative to the monitored persons, the percentage of exceedances of the regulatory dose limits is similar in both work categories.

For both work categories, there is a common result for the dose distribution: with an increasing effective dose or hand equivalent dose, the proportion of persons in the respective dose interval decreases. In the dose distribution in production and distribution of radioisotopes, it can be observed that the relative share with a dose value of 0 mSv decreases and more persons are registered in the dose intervals >0–1.5 mSv for the effective dose and >10 mSv for the hand equivalent dose.

Furthermore, it can be seen, that the relative shares in the dose distribution of the effective dose and hand equivalent dose in production and distribution of radioisotopes change significantly. The reason could originate from restructuring the work categories. The dose distribution in nuclear medicine does not show any trend. Overall, it is evident that in the dose distributions for the effective dose and hand equivalent dose in nuclear medicine, no massive changes were observed. Such not existent changes within the dose distribution must be highlighted: the number of patients must have been increased significantly and the range of radiopharmaceuticals has changed considerably. Unfortunately, there are currently no validated and publicly available datasets showing the number of patients, radionuclide(s), administered activity and location of nuclear medicine departments nationwide. It would be highly interesting to establish a normalised dose to show the correlation between the handled activity and the effective dose.

There have been reports about the nuclide-specific normalised dose for certain radionuclides in specific nuclear medicine departments. McCann *et al* (2023) reported the normalised dose for ^{68}Ga in a multi-centre study for hand exposures. UNSCEAR (2022, p 93) presented data for ^{18}F, ^{99m}Tc, $^{188/186}$Re and ^{153}Sm for certain procedures during hand exposure. Andriulevičiūtė *et al* (2022, p 6) and Wrzesień (2018, pp 544, 545) presented data for ^{99m}Tc and ^{18}F hand exposures, respectively. Carnicer *et al* (2011, p 1280) showed data for ^{18}F and ^{99m}Tc hand exposures within the ORAMED-project. So far only normalised doses for the hand equivalent dose are reported. The normalised dose is highly dependent on the handled radionuclide and the protection measures. However, it can be seen that significantly more persons have a hand equivalent dose >3 mSv in nuclear medicine than in production and distribution of radioisotopes. This is a paradox: the overall handled activity is many times higher in a production facility than in a single nuclear medicine department. The reasons for this observation cannot be pointed out at the moment. In nuclear medicine the manner, how unshielded activity is repeatedly used within the near vicinity of extremities or a lacking radiation protection culture (European Commission 2010, p 5) could be possible reasons for this observation. Shielding and distancing tools (e.g. master slave manipulators, process cells and gloves boxes with specific in-cell equipment or engineered forceps) are frequently used in production facilities, while nuclear medicine personnel cannot use such tools when operating close to unsealed sources and patients, which can be sources themselves. Therefore, research regarding this aspect of radiation protection should be performed. At the moment one cannot elaborate, whether protection measures resulted in a change of the dose distribution. SSR is not informed about specific optimizations by the licensees. Therefore, a link between dose distribution and optimization measures cannot be stated.

No statements can be made about trends in the eye lens equivalent dose nor committed effective dose from internal exposure. So far, the dataset features too few figures.

Due to a left shift in the dose distribution for the effective dose and hand equivalent dose reviewing only the mean and median values will mislead. Following the recommendation by Vogt (2022, p 97) all three statistics shall be presented: mean value, median value and dose distributions.

4.2. Aiming for practical radiation protection

The focus on dose development in the production and application of radiopharmaceuticals in Germany shall be on how practically doses will be minimized.

First of all, the correct positioning of dosimetry detectors is important. Whole-body dosimeters must be located on the torso. The finger ring dosimeter for extremity monitoring must be positioned at the most exposed location, but for standardization purposes, the base of the index finger of the non-dominant hand towards the palm is sufficient (Carnicer *et al* 2011, p 1282, Kyriakidou *et al* 2021, p 8). Depending on the radionuclide, incorrect measurement positions can pose underestimated doses. Despite the findings by Cunha *et al* (2023, p 31) are not representative (but could be a first indicator), one can see, that the wearing positions of finger ring dosimeters vary. Donadille *et al* (2008, p 65) remarked, that there are significant discrepancies between the mean annual doses reported in national dosimetric databases and dosimetry services, and the doses measured in pilot research studies. This demonstrates that current methods of dose monitoring underestimate the real radiological risk. Kollaard *et al* (2021, pp 12–14) present an overview for some currently intensively used radiopharmaceuticals and the possible dose ratio for hand exposure. It is evident, that the dose ratio is dependent on the position of the dosemeter and the most exposed part of the hand. ICRP (2009, p 181) suggested, if the most exposed part of the hand cannot be monitored, a multiplying factor or dose ratio may be applied to doses recorded by finger ring dosimeters worn in the middle finger of the dominant hand.

General radiation protection measures must be followed (Vogt 2022, pp 91, 92):

- Reduction of the time of stay in the radiation field,
- Increase the distance to the radiation source,
- Use of shielding,
- Control of the breathing air,
- Activity minimization.

Specific measures must be considered (ICRP 2009, pp 181,182, Lecchi *et al* 2016, p 2281, Kollaard *et al* 2021, pp 14–19, Vogt 2022, pp 91,92 Bouchareb *et al* 2023, p 8):

- Checking and limiting the dose rate for the whole body, hands, and eye lenses,
- Sufficient shielding of the workplace itself and for neighboring workplaces, especially vials and syringes,
- Prevention of direct contact with activity-carrying media and/or using forceps and use prior venous cannulation,
- Use of shielded distancing tools,
- Wearing protective clothing and frequent contamination checks of the body or glove surfaces and workplaces,
- Automation of processes (e.g. injection and dispensing),
- Use of protective eyewear as shielding and/or contamination protection,
- Checking workplaces with a checklist,
- Workload sharing of the personnel,
- Implementing regular risk assessments, especially before introducing new unsealed radiopharmaceuticals,
- Rotation of personnel to minimize the likelihood of higher doses,
- Adequate training with non-radioactive substances before handling active substances.

Cunha *et al* (2023, p 35) demonstrate that the current use of protective measures in nuclear medicine depends on handled nuclide and task (e.g. preparation, dispensing, administration). The use of protective measures is not uniformly implemented.

Audit tools and inspection manuals developed by Donzé *et al* (2022) and Vogt (2022) should be used by radiation protection supervisors to optimize the exposure situation even below regulatory limits.

4.3. Comparison to other countries

Other research on this topic does not always follow the same methodology, thus preventing comparisons. Mainly the population can vary: a differentiation between monitored persons and measurably exposed persons is made.

The production and distribution of radiopharmaceuticals are rarely analyzed. An exemption in this regard is the differentiation between nuclear medicine, nuclear medicine (PET/CT), radiotherapy, cyclotron operation and radiopharmaceutical distribution by Romallosa Dean *et al* (2022). Bouchareb *et al* (2023), Sahmaran *et al* (2022) and Martins *et al* (2007) follow another method: administrative, medical doctor, nuclear medicine technician, physicist and more occupations in nuclear medicine are analyzed separately.

Noh *et al* (2023) chose a different approach: the dataset was segmented by various properties. The dataset was partitioned into the worn passive dosemeter/badge, sex, age, and annual mean effective dose by the first reported year of radiation workers. Segmenting the dataset by these properties should be considered for future research.

It is important to note that some publications mix up fields e.g. radiology, nuclear medicine, teletherapy, and brachytherapy. However, this approach is not optimal since each field has its unique exposure scenarios. As a result, there may be significant variations in dose development between them, as demonstrated by Weizhang *et al* (2005). E.g. Hernández *et al* (2001) include nuclear medicine, radiotherapy and radiology within the medical field.

Hence, it can be concluded, that sharp conditions are crucial for a worldwide comparison. Crucial for a comparison between countries are the validated datasets from National Dose Registers with strict characteristics for datasets. On a european level, the European Platform for Occupational Radiation Exposures (ESOREX Platform—www.esorex-platform.org) offers a variety of datasets. This database allows a quite detailed comparison of the same occupation between different states as well as different occupations within one state (ESOREX Platform 2016). A comparison and definition of occupation profiles on a european level can at least support standardization. Comparisons shown by Kyriakidou *et al* (2021) underline the need for harmonization in the field of National Dose Registers.

Comparing data by Alashban and Shubayr (2021, p 54) and Rahman *et al* (2016, p 56) with the findings from this paper it can be shown, that Germany's mean effective dose of 0.92 mSv (mean dose from 1997 until 2021) of measurably exposed personnel in nuclear medicine is significantly lower than most of the compared countries. In this regard, it is clear that this nationwide study, which uses data from 25 years, has one of the longest timeframe datasets available.

For the production and distribution of radioisotopes there is no data for the effective dose for measurably exposed personnel worldwide available. In Germany the mean effective dose from 1997 until 2021 for measurably exposed personnel in production and distribution of radioisotopes accounts to 1.12 mSv.

Data for monitored persons from 1975 to 2014 by UNSCEAR (2022) show worldwide a decrease for the mean effective dose in production and distribution of radioisotopes and nuclear medicine from 2.2 mSv to 0.8 mSv (UNSCEAR 2022, p 111) and 1.0 mSv to 0.4 mSv (UNSCEAR 2022, p 96), respectively. The dataset presented in this paper can be characterized by a mean effective dose in production and distribution of radioisotopes and nuclear medicine from 1997 until 2021 with 0.41 mSv and 0.18 mSv, respectively.

4.4. Optimization according to as low as reasonably achievable (ALARA)-principle

With the introduction of the optimization principle, two concepts are now available: an individual-related approach guarded by dose limits and a source-related approach accompanied by dose constraints (Kong *et al* 2021, p 352). In compliance with § 72 Radiation Protection Ordinance, the radiation protection executive has to check, whether implementing dose constraints is a suitable measure for optimization.

The German Commission on Radiological Protection (Strahlenschutzkommission) recommends the implementation of dose constraints for the medical field below the ordinance level. Optimization shall be additionally achieved by technical and administrative measures. Measures shall be observed by detailed analysis of the handling process with local dose rate measurements. For radionuclide laboratories not within the medical field dose constraints are not recommended. Already existing recurring training of personnel shall be continued to enhance awareness. Handling radioactive substances in e.g. glove boxes or process cells already minimize the incorporation risk. The most relevant exposure is not the gamma dose rate but the exposure by beta- and alpha-emitters. Typically beta- and alpha-emitters without significant gamma emissions are efficiently shielded when handling radionuclides in glove boxes and/or process cells. Dose values above the usual values shall be reported to the competent authority and causes shall be determined. (Strahlenschutzkommission 2014, pp 6–8, 19–23)

As Romallosa Dean *et al* (2022, p 11) report while handling radiopharmaceuticals due to largely inhomogeneous fields a wide range of doses can be received. This publication supports this sighting, considering that monitoring the whole-body dose must be accompanied by monitoring the hand equivalent dose for some personnel. For aiming for the complete picture and a more effective control of occupational exposures whole-body and extremity monitoring is essential (Romallosa Dean *et al* 2022, p 11).

This paper emphasizes the existence of individuals with occupational exposure, who face the possibility of surpassing regulatory dose limits. At least for nuclear medicine, this trend is shown by Romallosa Dean *et al* (2019, p 86) too. According to this paper and research conducted by Romallosa Dean *et al* (2019, p 85), Ahmad *et al* (2020, p 49) and Kong *et al* (2021, p 353), most people receive low or undetectable levels of radiation. Only a small number of individuals are exposed to higher doses. Following the ALARA principle, the radiation protection supervisors, without regard to nuclear medicine or the production and distribution of radioisotopes, shall implement balanced measures.

Communicating the measures as well as the level of risk is key to reaching awareness. Michel *et al* (2018, p 7) and Völkle (2021, p 57) developed a traffic light model, which comprises the lower acceptance level, the in-between optimization area and the upper acceptance level, where measures are needed. This model should be used for communicating such risks.

Comparing the mean effective dose in the production and distribution of radioisotopes and nuclear medicine, respectively 0.84 mSv and 0.75 mSv in 2021, with the mean natural radiation exposure of the population of, 2.1 mSv per person and year (Bundesamt für Strahlenschutz 2022, p 5), the 'additional contribution' due to occupational exposure is at a low level.

A reduction to 0 mSv is technically nearly impossible and draws an intransparent picture of exposure situations. Handling radioactive substances can ultimately induce an exposition. Hence, implementing dose constraints may not necessarily provide the optimal solution for exposure optimization. Radiation protection executives have to check, whether an implementation is a suitable measure for each specific handling situation. Practical and target-aimed measures and a transparent radiation protection culture are probably more efficient, but unfortunately not quantifiable by measurement. A focus on the reasonably in ALARA and 'taking into account economic and societal factors' (ICRP 2007, p 89) shall be the focus for the next decade.

5. Conclusion

Radiopharmaceuticals have become an important column in clinical diagnostics and therapy. Over a period of 25 years, this research displays mean, median effective doses and hand equivalent doses as well as the corresponding dose distributions for the application and production of radiopharmaceuticals. The figures display the effort for optimizing exposure situations done by radiation protection professionals and radiation protection society.

Most importantly it can be seen, that during the last three decades the effective dose decreased while handling in nuclear medicine and production and distribution of radioisotopes. The hand equivalent dose in nuclear medicine increases steadily. A distinct and discernible trend for the hand equivalent dose in production and distribution of radioisotopes cannot be seen at the moment. Handling radioactive substances lead to overexposures for a minority of occupationally exposed workers in nuclear medicine and production and distribution of radioisotopes.

The current radiation protection principles in Germany and their rules predominantly work well. The development of the hand equivalent dose shall be carefully watched during the next decade. Continuing with balanced radiation protection measures according to the ALARA-principle exposure situations will be optimized.

Data availability statement

All data that support the findings of this study are included within the article (and any supplementary files).

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