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RENEB Inter-Laboratory Comparison 2021: Inter-Assay Comparison of Eight Dosimetry Assays

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Tools for radiation exposure reconstruction are required to support the medical management of radiation victims in radiological or nuclear incidents. Different biological and physical dosimetry assays can be used for various exposure scenarios to estimate the dose of ionizing radiation a person has absorbed. Regular validation of the techniques through inter-laboratory comparisons (ILC) is essential to guarantee high quality results. In the current RENEB inter-laboratory comparison, the performance quality of established cytogenetic assays [dicentric chromosome assay (DCA), cytokinesis-block micronucleus assay (CBMN), stable chromosomal translocation assay (FISH) and premature chromosome condensation assay (PCC)] was tested in comparison to molecular biological assays [gamma-H2AX foci (gH2AX), gene expression (GE)] and physical dosimetry-based assays [electron paramagnetic resonance (EPR), optically or thermally stimulated luminescence (LUM)]. Three blinded coded samples (e.g., blood, enamel or mobiles) were exposed to 0, 1.2 or 3.5 Gy X-ray reference doses (240 kVp, 1 Gy/min). These doses roughly correspond to clinically relevant groups of unexposed to low exposed (0–1 Gy), moderately exposed (1–2 Gy, no severe acute health effects expected) and highly exposed individuals (>2 Gy, requiring early intensive medical care). In the frame of the current RENEB inter-laboratory comparison, samples were sent to 86 specialized teams in 46 organizations from 27 nations for dose estimation and identification of three clinically relevant groups. The time for sending early crude reports and more precise reports was documented for each laboratory and assay where possible. The quality of dose estimates was analyzed with three different levels of granularity, 1. by calculating the frequency of correctly reported clinically relevant dose categories, 2. by determining the number of dose estimates within the uncertainty intervals recommended for triage dosimetry (±0.5 Gy or ±1.0 Gy for doses <2.5 Gy or >2.5 Gy), and 3. by calculating the absolute difference (AD) of estimated doses relative to the reference doses. In total, 554 dose estimates were submitted within the 6-week period given before the exercise was closed. For samples processed with the highest priority, earliest dose estimates/categories were reported within 5–10 h of receipt for GE, gH2AX, LUM, EPR, 2–3 days for DCA, CBMN and within 6–7 days for the FISH assay. For the unirradiated control sample, the categorization in the correct clinically relevant group (0–1 Gy) as well as the allocation to the triage uncertainty interval was, with the exception of a few outliers, successfully performed for all assays. For the 3.5 Gy sample the percentage of correct classifications to the clinically relevant group (≥2 Gy) was between 89–100% for all assays, with the exception of gH2AX. For the 1.2 Gy sample, an exact allocation to the clinically relevant group was more difficult and 0–50% or 0–48% of the estimates were wrongly classified into the lowest or highest dose categories, respectively. For the irradiated samples, the correct allocation to the triage uncertainty intervals varied considerably between assays for the 1.2 Gy (29–76%) and 3.5 Gy (17–100%) samples. While a systematic shift towards higher doses was observed for the cytogenetic-based assays, extreme outliers exceeding the reference doses 2–6 fold were observed for EPR, FISH and GE assays. These outliers were related to a particular material examined (tooth enamel for EPR assay, reported as kerma in enamel, but when converted into the proper quantity, i.e. to kerma in air, expected dose estimates could be recalculated in most cases), the level of experience of the teams (FISH) and methodological uncertainties (GE). This was the first RENEB ILC where everything, from blood sampling to irradiation and shipment of the samples, was organized and realized at the same institution, for several biological and physical retrospective dosimetry assays. Almost all assays appeared comparably applicable for the identification of unexposed and highly exposed individuals and the allocation of medical relevant groups, with the latter requiring medical support for the acute radiation scenario simulated in this exercise. However, extreme outliers or a systematic shift of dose estimates have been observed for some assays. Possible reasons will be discussed in the assay specific papers of this special issue. In summary, this ILC clearly demonstrates the need to conduct regular exercises to identify research needs, but also to identify technical problems and to optimize the design of future ILCs.

INTRODUCTION

In the course of large-scale radiological or nuclear incidents as a result of accidents (e.g., nuclear power plant explosion) or intentional malicious activities (e.g., dispersion of a radioactive source or the detonation of an improvised nuclear device), rapid screening of dozens, hundreds or even thousands of individuals will be necessary (*1*).

Preparation for such large-scale events requires an early assessment of individual radiation-exposure estimate and clinical outcome prediction to direct and reserve limited clinical resources and infrastructure to those in need. In principle, three groups must be identified during the initial steps of medical management: 1. The first group are individuals who believe they have been exposed, but have not actually received radiation doses and do not need medical care (so called ''concerned citizens''). The identification of these individuals allows saving limited clinical resources. 2. The second group comprises individ-

uals exposed to lower levels of radiation, not requiring immediate care; however, increased risk for late health effects demands surveillance over the next decades. 3. The third group includes highly exposed individuals in need of early treatment and immediate hospitalization to maximize their chances of survival and recovery.

Knowledge of individual radiation exposure is an important aspect of identifying the above groups and supporting medical care for individuals exposed to radiation (*2–4*). Recent discussions have identified limitations of this approach (deducing acute health effects from dose estimates), but nonetheless argue not against but specify the value of individual dose estimates for this purpose (*5–8*).

Conventional physical dosimeters, commonly used by radiation professionals, will not be present in all the potential exposure scenarios mentioned above, especially if the public is involved. Biological responses to radiation can include several cytogenetic changes. These comprise e.g., the formation of dicentric chromosomes (DCA), micronuclei employing the cytokinesis-block micronucleus assay (CBMN), stable translocations identified by whole chromosome painting applying fluorescence in-situ hybridization (FISH) techniques (translocation assay, FISH) as well as chromosome fragments detected via premature chromosome condensation (PCC). Furthermore, molecular changes quantified at the DNA- (DNA repair foci, gH2AX) or RNA-level (gene expression, GE) represent individual biological markers of exposure. Physical dose estimates of local exposure using smartphone glass or electronic components like resistors or tooth enamel (via optically or thermally stimulated luminescence, LUM or electron paramagnetic resonance, EPR) add to the reconstruction of individual radiation exposure and, thus to the weight of knowledge around the clinical outcome prediction of acute health effects occurring days or weeks after exposure (*9, 10*).

DCA is the most established ''gold standard'' biodosimetry technique for the detection and quantification of ionizing radiation exposure (*11*), due to its high specificity and sensitivity, as well as many years of validation, inter-laboratory comparisons and testing in real life radiation incidents. However, analysis of this assay is time consuming and several different approaches to increase the throughput are currently implemented for large scale accident situation, including triage-mode scoring (*12–15*), ''QuickScan'' dicentric chromosome analysis (*16, 17*), networking between biodosimetry laboratories (*18*), telescoring (*19*) and automation (*20–24*). Besides DCA, the CBMN assay is a suitable assay for biodosimetry, especially regarding triage biodosimetry, due to its quick scoring/automation abilities (*21, 25*). A prerequisite for running all assays is the availability of calibration curves for appropriate radiation qualities that enable aberration yields to be converted to dose estimates. Calibration curves or single calibration samples are usually missing for evolving assays such as the GE, gH2AX, EPR and LUM assays and these were thus provided to the teams during this inter-laboratory comparison (ILC) exercise.

Inherent characteristics of emerging assays such as GE and gH2AX allow for early and high-throughput diagnostic. This is partly driven by automation and multiplexing capabilities, making these assays attractive for further examination and development (*7, 26*). However, these assays measure transient signals formed in irradiated cells, which change rapidly over time (*27, 28*). This restricts the diagnostic window to a few days post exposure and challenges the dose estimation by altering signals over time (*27, 29*). Given the emphasis on rapid triage in a large-scale incident, these disadvantages may still be acceptable, especially when considering a two-tiered system where initial triage using molecular assays is followed by more accurate chromosome dosimetry for those identified as most highly exposed (*30*).

Physical dosimetry methods include EPR, OSL and TL and can be used on biologically derived materials (bone, teeth) or non-biologically derived materials (such as inorganic materials carried by or worn by the individual, including electronic devices and clothing) (*9, 31–35*). However, as an example for EPR, the UV-sensitivity, minimum required sample size and mass, expenses (equipment), mechanical stress (drilling, grinding), as well as the quality of gained information (measurement of a local but not necessarily a whole-body exposure) have to be considered (*36*). Procedures to overcome unstable and non-radiation-induced signals are needed, but such problems may be offset by the rapidity with which initial triage doses can be reported. Summary reports of how best biodosimetry methods can be used together with physical dosimetry methods for initial-phase triage dosimetry after acute exposure are available (*10*).

RENEB (Realizing the European Network for Biodosimetry and Retrospective Physical Dosimetry) was established with support from the European Commission (EURATOM FP7, GA 295 513) from 2012–2015. In 2017, after completion of the initial project, RENEB transformed into a legal association (redefined as ''Running the European Network for Biological Dosimetry and Retrospective Physical Dosimetry'') to continue its purpose: sustain laboratory skills for providing dose estimations in situations of intentional (e.g., terrorist or military act) or unwanted release of radiation (e.g., nuclear power plant accident) to support medical management decision making. RENEB has organized various ILCs and field comparison exercises for preparedness reasons (*14, 37–46*).

The performance of quality controlled ILC exercises using ex vivo irradiated, blind coded samples are a common measure in RENEB to validate assay performances as well as laboratories. The RENEB ILC 2021 presented here in this inter-assay comparison article and followed by assay specific publications (*47–51*) has several unique features: 1. Comparing, in parallel, established cytogenetic assays (DCA, CBMN, PCC, FISH) with molecular biology (GE, gH2AX) and physical dosimetry assays (EPR, LUM); 2.

Providing skilled laboratories outside the RENEB association the opportunity to participate. Hence, a broader range of dose estimation capabilities spanning three continents are encompassed by this series of publications; 3. Taking advantage of many participating teams and laboratories receiving the samples irradiated at the same time allowing the identification of inconsistencies and providing opportunities for improvements; 4. Simulating a worst-case situation in preparation of future scenarios that informs and identifies difficulties, other than those related to the assays (e.g., delivery hurdles), which are important to address and should lead to future improvements.

As the first of a series, this manuscript provides more general information about the exercise (e.g., delivery hurdles and times), including details on the radiation exposure of the samples so that all subsequent manuscripts may refer to it to avoid redundancies. This manuscript also compares assay performances in three ways. First, the lowest granularity was achieved by calculating the frequency of correctly reported, clinically relevant dose categories per assay. According to MULTIBIODOSE guidelines, these groups comprise unexposed-low exposed (0–1 Gy), medium exposed (1–2 Gy) requiring in general no immediate care, and highly exposed (>2 Gy) individuals who may be in need of hospitalization and early and intensive medical care (*52*). Second, by determining the number of dose estimates considering the ±0.5 Gy interval for reference doses <2.5 and ±1.0 Gy for reference doses >2.5 Gy, as recommended for triage dosimetry (*25*), an intermediate granularity was chosen. Third, at the highest level of granularity, we compared the absolute difference (AD) of estimated doses relative to the reference doses among teams and assays.

The analysis of cytogenetic assays revealed a systematic shift towards higher dose estimates, while dose estimates of other assays were partly biased by methodological issues and limits. These challenges will be addressed in subsequent publications within this special issue (*47–51*), with each focusing on results of a specific assay, except the PCC assay where only two teams participated and the physical dosimetry assays (EPR, OSL, TL), which will be presented in later publications. However, within this inter-assay comparison manuscript, these first dose estimates were analyzed unfiltered (except for elimination of redundantly reported dose estimates) to simulate a scenario, where early (possibly partly biased) dose estimates are required to support immediate medical management. The final manuscript in this series will provide a perspective on reevaluated dose estimates compared over all assays and the lessons learned in the context of previous inter-laboratory exercises (*53*).

MATERIALS AND METHODS

General Description of Samples, Irradiation Procedures and Samples' Distribution

For biological dosimetry-based assays, peripheral blood was drawn from two healthy human volunteers using 2–3 ml tubes (Becton Dickinson, Germany) to cover inter-individual variance. A 30-year-old female individual provided blood for calibration samples and a 32-year-old male provided blood for blinded coded samples. Blood was taken with informed consent and the approval of a local ethics committee (Bayerische Landesärztekammer, Munich, Germany). Pre-exercise, calibration samples for molecular biological assays were sent to all GE (except one) and gH2AX teams for the generation of calibration data. For cytogenetic assays no calibration samples were distributed in advance and labs were asked to use their own established calibration curves for dose estimates. About one month after sending calibration samples blinded coded samples were distributed to all teams. For physical dosimetry assays different materials were collected and irradiated. These comprised tooth enamel, watch glass and display glass for the EPR assays and whole smartphones (for instance iPhone and Samsung types) for OSL and TL assays. Surface mount resistors (SMRs) from irradiated smartphones were analyzed with OSL while samples of protective glass (assumed to be made from Gorilla® Glass) were tested with both OSL and TL. Calibration samples were provided to all EPR and LUM teams prior to the exercise.

All materials (e.g., blood, tooth enamel as well as inorganic materials such as glass) were irradiated top-down at room temperature with single doses in a Maxishot SPE X-ray cabinet (Yxlon, Hamburg, Germany) using 3 mm beryllium and 3 mm aluminum filters, an accelerating potential of 240 kVp and a 13-mA electron beam current (Fig. 1). At these values, the generated X-ray radiation had a half-value layer (HVL) for copper of 0.630 ± 0.025 mm (approximating to a mean photon energy of 75 ± 5 keV), a field size of about 15 × 15 cm^2 in the sample plane at a 60 cm source distance and a kerma in air rate of approximately 1.0 Gy/min. For dosimetry, a UNIDOS webline 10021 dosimeter using a Farmer chamber TM30010-1 calibrated in kerma in air with Co-60 (PTW, Freiburg, Germany) was used, which stops the irradiation when a predefined dose value is reached.

For non-water equivalent samples, kerma in air $K_{air,X\text{-}ray}$ for the X-ray irradiation was used, which was calculated by

$$K_{air,}X - ray = k_q \cdot K_{air,Co-60}$$

according to (*54*) using a correction factor for the radiation quality k_q and the reference kerma for Co-60 $K_{air,Co\text{-}60}$ measured by the dosimeter.

For biological samples, dose in water $D_{water,X\text{-}ray}$ for the X-ray irradiation was estimated according to DIN 6809-5 by

$$D_w = k_{a->w} \cdot t_{w,a}{}^{en} \cdot K_{air,X-ray}.$$

The correction factors are presented in Table 1. All correction factors were estimated for the X-ray irradiation by averaging the correction factors of the standard radiation qualities TH140 and TH150, because its HVL lies between the corresponding HVL (HVL_{Copper} (TH140) = 0.43 mm and HVL_{Copper} (TH150) = 0.82 mm; DIN 6809-4).

A delay of 1 s in the switch-off process of the X-ray source leads to an additional dose contribution of about 17 mGy. This dose was not considered for the reported doses, since it contributes 1.7% (at 1 Gy) or less additional exposure to our irradiated blinded coded samples and better reflects a real radiation scenario in an early phase.

Dose homogeneity of the radiation field was determined by using Gafchromic®EBT3 films (Ashland Advanced materials, Bridgewater, NJ), which were calibrated in advance using the X-ray source. For the field dimensions used, dose homogeneity was 1.5%, which contributes to an additional dose variance between irradiated biological or physical samples.

Finally, the overall uncertainty for kerma in air $K_{air,X\text{-}ray}$ and dose in water D_w can be calculated by Gaussian error propagation to 1.9% and 4%, respectively, representing a confidence level of 68%.

In total, three independent methods were used for verification of the absolute irradiation dose (kerma in air): 1. Regular calibration of the Farmer chamber used for dose monitoring was carried out by the manufacturer PTW (Freiburg, Germany). Calibration factors are given with an uncertainty of 2.2%; 2. Comparison of the dosemeter used

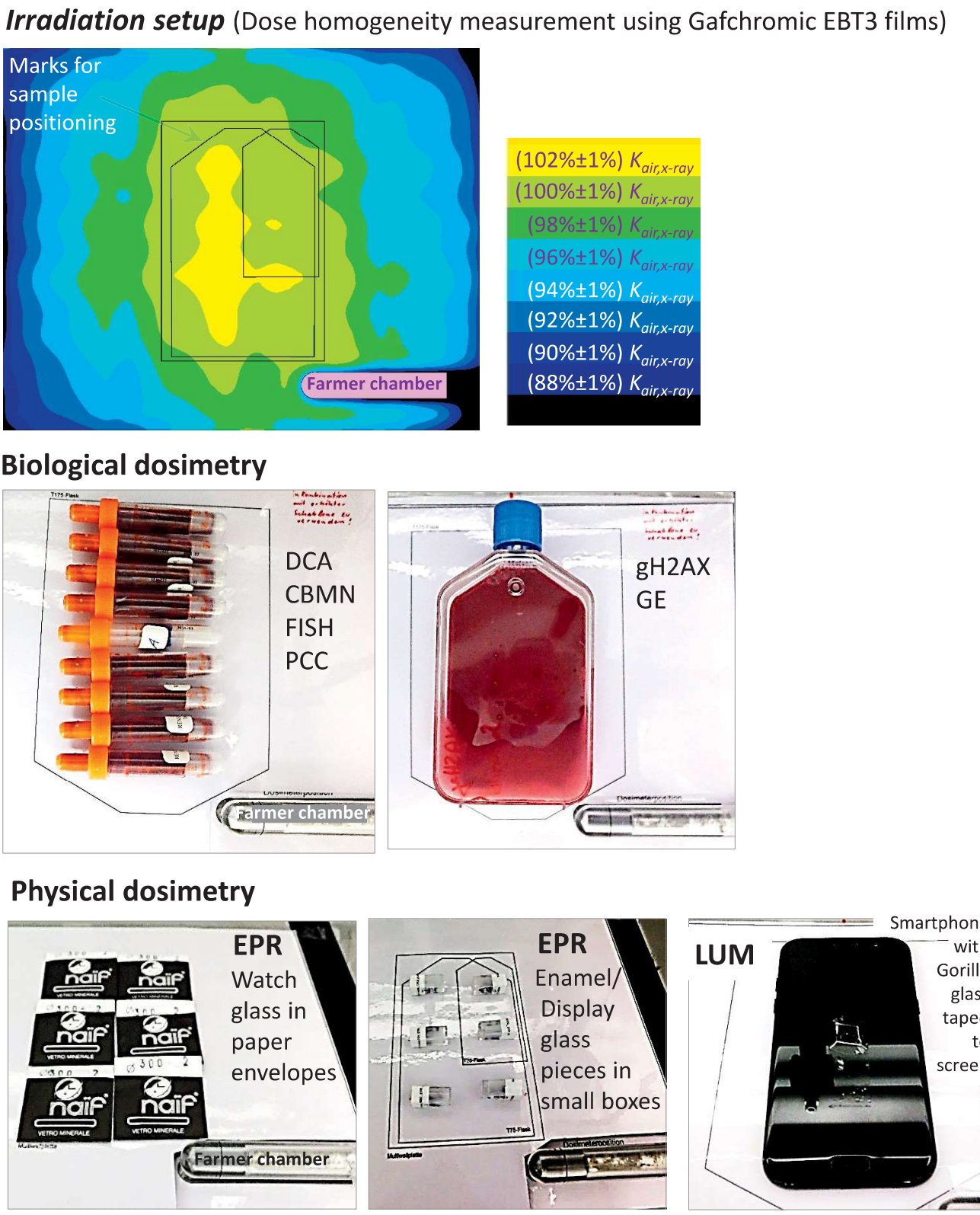

FIG. 1. Irradiation setup for the RENEB inter-laboratory comparison 2021 involving eight dosimetry Assays. Kerma homogeneity was determined using Gafchromic EBT3 films (mean of 5 irradiations shown. Homogeneity ±1.5% in the relevant field areas, in which samples were placed, reproducibility ±0.5%). Irradiation time and thus the dose was controlled by a Farmer chamber TM30010-1 placed next to all irradiated materials.

TABLE 1
Correction Factors for Calculation of Kerma in Air $K_{air,X\text{-}ray}$ and Dose in Water D_w for the X-ray Radiation Used

Correction factor for	Variable	Mean value for TH140 and TH150	Uncertainty on 68% confidence	Reference
Radiation quality	k_q	0.98	1.10%	Calibration sheet 10/2020 by PTW
Change of medium at 5 cm depth (air-> water)	$k_{a->w}$	1.025	0.50%	DIN 6809-5 (Appendix B)
Ratio of mass energy absorption coefficient water/air at 0 cm depth	$t_{w,a}^{en}$	1.054	3%	DIN 6809-5 (Appendix B)

during the exercise (Farmer chamber TW 30010 with UniDos webline 10021, PTW, Germany) with dosemeters of the group for ''external and internal dosimetry'' of the BfS (Farmer chamber TW 30010 and Farmer chamber TM23331-261 with UniDos E, PTW, Germany) ahead of the exercise. Here, kerma in air dose measurements using the same X-ray source for defined irradiation times of 120 s agreed within ±4% for all dosemeter setups (and within 1% when the two Farmer chambers TW 30010 were used); 3. Calibration using thermoluminescent dosimeter (TLD) chips from the KIT (Karlsruhe Institute for Technology, Department for ''Sicherheit und Umwelt – Festkörperdosimetrielabor''). Three TLD chips were used for the monitoring of three blood irradiations during the ILC with ''dose in water'' of 1.2 Gy (2×) and 3.5 Gy (1×). Here, TLDs were irradiated in empty blood vials, sent back to and analyzed by KIT. TLDs were calibrated against kerma in air with Cs-137. The analysis of the TLDs resulted in ''kerma in air'' of 1.3 Gy and 1.4 Gy for the low dose and 3.9 Gy for the high dose irradiation. Using the presented correction factors in Table 1, the ''kerma in air'' values correspond to ''dose in water'' values of 1.4 Gy, 1.5 Gy and 4.2 Gy and thus a systematic overestimation by 25%. TLDs provided by the KIT are not calibrated for the geometry and energy spectrum of the ILC irradiation. Thus, the KIT did not provide uncertainties for the TLD dose assessment. However, the overestimation can be explained by the missing photon energy correction of the TLDs used by KIT (TLD-700, Harshaw). For these TLDs a relative response of 1.35 for TH140 and 1.04 (Cs-137) compared to Co-60 is reported (Schwahofer et al. 2016). Thus, an overestimation of 30% is expected for the radiation quality (roughly TH140) used in this ILC compared to Cs-137 radiation used by KIT, which is consistent with the observed overestimation of 25% assuming that typical response uncertainty of single TLDs is about ±2.5%.

For this exercise, reference doses for irradiated glass samples (EPR and LUM assays) represent kerma in air while for all blood samples (cytogenetic and molecular biology-based assays) it is dose in water. However, dose estimation results from tooth enamel analysis (EPR assay) are reported in terms of enamel kerma and are not, therefore, directly comparable to doses from others assays. Enamel kerma has the advantage that participants can use their own calibration curves without having the necessity to know the characteristics of the X-ray beam used for the ILC or to define a correction factor to account for the energy dependence when results are expressed in air kerma. This approach is preferred for accident dosimetry (*10, 55*). At low-photon energy (<100 keV), depending on beam quality and enamel composition, large differences are observed between enamel kerma and air kerma ranging from a factor of 1 up to a factor of 11 (*56–63*). However, to compare reported kerma in enamel with the kerma in air reference values, the reported results were converted to kerma in air for the 240 keV X rays used for irradiation of the blinded samples. The conversion factor $k_{f,}$ defined as the ratio of kerma in enamel/kerma in air, was $k_f = 6.5$ and was calculated for the effective energy of the X rays (240 keV, HVL = 0.63 mm) using mass absorption coefficients (for elemental constituents of hydroxyapatite) given by NIST website (https://www.nist.gov/pml/x-ray-mass-attenuation-coefficients). For this ILC, participants have analyzed samples from the same tooth to avoid problems with variability of dose response linked to enamel composition. A detailed analysis of enamel data will be presented in a separate paper focused on EPR dose and will be not provided in this special issue.

After irradiation, samples were treated differently (assay dependent) and the shipment was performed by overnight express service as UN 3373 Biological Substance Category B (*11, 64*). Transport dependent temperature profiles and potentially undesired radiation exposures were monitored by adding temperature loggers (EL-USB-1, data-logger-store, Eichstetten, Germany) and TLD chips (TLD, Karlsruhe Institute of Technology) to the packages. All teams sent the temperature loggers and dosimeters back to the organizer for further analysis.

Sample Preparation and Analysis for the Different Biodosimetry Assays

Protocols for sample preparations and analysis for the six biological assays are described in the assay-related manuscripts of this series (*47–51*).

Collecting Data Regarding Dosimetry, Temperature and Undesired Radiation Exposure During Delivery

Several time intervals were determined to characterize the transport of packages to the participants and required time for laboratory work:

- *Delivery time to the laboratories*. This includes the delivery of samples at Bundeswehr Institute of Radiobiology (BIR) to the courier (FedEx) and the arrival of the samples at the participating institutions. This was recorded in the courier report. This time frame includes possible delays between the arrival of samples in the laboratories of the teams and the onset of laboratory work if reported.
- *Report time for dose estimates*. This comprises the interval between the start of the laboratory work and the reporting of the dose estimates via email. This was documented by the organizer via the receipt of the email sent by the teams.

Along with the reported dose estimates, most teams provided information regarding the level of priority given to the analysis of the samples during daily business. Not restricting participation to the highest level of priority ensured the participation of a larger number of laboratories. Dose estimates were requested to be reported within six weeks after sending samples from BIR. After that, the exercise was closed, and reference doses were communicated to all participants.

Statistical Methods

The accuracy of reported dose estimates was measured by calculating the absolute differences (AD) of estimated doses to their corresponding reference doses separately for each of the three blinded reference samples. As a second measure of dose estimate accuracy, we determined the number of dose estimates falling within the ±0.5 Gy interval for reference doses <2.5 Gy and ±1.0 Gy for reference doses >2.5 Gy, as recommended for triage dosimetry (*25*).

The radiation exposure level of samples corresponded to clinically relevant groups. Namely,

- identification of unexposed and low exposed individuals (0–1 Gy group, including the 0 Gy reference sample) is required, to avoid clinical resources being occupied by those who are concerned but not really exposed (''concerned citizens'');
- identification of medium exposed individuals (1–2 Gy group, including the 1.2 Gy reference sample), where mild acute effects (no hospitalization required) or, after several years, stochastic effects in adults might occur or become detectable using epidemiological methods;
- identification of highly exposed individuals (>2 Gy group, including the 3.5 Gy reference sample), who will probably suffer from the life-threatening acute radiation syndrome (ARS) days to weeks after radiation exposure.

All calculations were performed using SAS (release 9.4, Cary NC) or Excel (Microsoft Corporation,).

RESULTS

Transport of Packages

Transport of packages via courier (Global FedEx) and through international Customs was associated with several challenges:

1. Shipping on dry ice, recommended for GE analysis**,** is more complicated than with cool packs, because dry ice is classified as dangerous goods and strict shipping requirements and documentation are necessary. Any problems concerning documentation or package labeling can cause a complete stop to transportation and in some instances a high fine. Also, transportation expenses are much higher for dangerous goods such as dry ice. Delivering blood cells in a specific (RLT) lysis buffer for RNA isolation or even RNA aliquots (vials should be frozen before delivery) on wet ice proved to be sufficient instead of sending on dry ice in this and previous exercises.
2. Shipping lithium-ion batteries (e.g., mobile phones) followed dangerous goods regulations was a challenge. Only a certain number (weight) of batteries can be transported using the same package. This must be considered when sending irradiated smartphones containing unremovable batteries. Communication with the local distributor of the courier company is recommended to get information about their actual interpretation of regulations.
3. In emergency situations the infection status of the blood donors are usually unknown, therefore for RENEB exercises it was decided for safe transport to send blood samples according to the regulations for dangerous goods (Division 6.2 - infectious substances) and assigned them to UN3373 category B using packaging instructions P650-4.
4. Sometimes packages were not delivered by the courier, because their employee couldn't find the destination, but the address had not changed. Changing to another courier caused comparable difficulties and did not contribute to a solution. Persistent calling was the only strategy, but packages arrived delayed.
5. Limited space on the digital shipping documents for labelling the packages' address stickers sometimes caused problems at the target destination specifying the correct laboratory in a huge institution and a corresponding extensive address. Adding a label with the complete address on the packages solved that problem only partly, because courier personnel usually focused on the digital information presented on their hand-held device for transport documentation and did not notice complete addresses written on the packages.
6. Sending back temperature loggers outside the EU caused problems with Customs in different countries when estimated values between shipping invoice and pro forma invoice (e.g., 1 € vs. 2 €) differed. Also, a value of 0 € on shipping documents was not accepted.
7. Sending packages ahead for training purposes (e.g., packages containing calibration samples) proved an efficient measure to smooth the interface with the courier service and resulted in the successful delivery of most (98%, 49 out of 50 packages) but not all packages containing the blinded coded samples (one package was in transit for one month).
8. To avoid or minimize unwanted irradiation, the tags of No Examination with X ray could be attached to each package.
9. Assistance by experienced shipment companies is advisable to ensure that the transport runs as smoothly as possible.

Temperature Profiles and Radiation Exposure During Transport

For the calibration samples (sent in May 2021), temperatures ranged from 10–18°C when using wet ice (i.e., gene expression or gH2AX assays) and were approximately 20°C when sending samples at ambient temperature (i.e., EPR). For the blinded coded samples (sent in June 2021) temperatures remained around 10°C (±8°C) when using wet ice and 18–23°C for the transport at ambient temperature. None of the TLD chips recorded an additional radiation exposure during transport.

Participants and Contributions

Irradiated samples were sent to 40 scientific institutions and slides or microscopic images only were sent to another one or six institutions, respectively. These added up to 46 involved scientific institutions, representing 27 nations located on three continents [Europe, North America, Asia (Table 2)]. Initially, 86 teams requested participation, performing either the DCA (n = 33), CBMN (n = 16), FISH (n = 7), PCC (n = 3), gH2AX (n = 6), GE (n = 8), EPR (n = 6) or LUM (n = 7) assay for dose assessment. However, one EPR team delivered dose estimates after the publication of the reference doses. These latter data will be included in the separate publications but not considered in

TABLE 2
Participating Institutions and their Contributions (Employed Assays) to the Exercise

No.	Institution	Nation (n = 27)	Biological dosimetry						Physical dosimetry	
			Cytogenetic assays				Molecular Biology			
			DCA	CBMN	FISH	PCC	gH2AX	GE	EPR	LUM
1	Institute of Nuclear Chemistry and Technology, Warsaw, Poland	Poland	x	x		x	x	x		
2	National Centre of Radiobiology and Radiation Protection, Sofia, Bulgaria	Bulgaria	x	x	x		x			
3	National Public Health Center, Department of Radiobiology and Radiohygiene, Budapest, Hungary	Hungary	x	x			x	x		
4	Bundeswehr Institute of Radiobiology, Munich, Germany	Germany	x	x			x	x		
5	Institut de Radioprotection et de Surete Nucleaire, Fontenay aux Roses, France	France	x		x				x	x
6	UK Health Security Agency, Radiation, Chemical and Environmental Hazards Division, Oxfordshire, UK	England	x			x	x	x		
7	Korea Institute of Radiological & Medical Sciences, Lab of Biological Dosimetry, Seoul, Korea	Korea	x	x	x					
8	Bundesamt für Strahlenschutz, Oberschleißheim, Germany	Germany	x	x			x			
9	IST/ Campus Tecnológico e Nuclear, Lisbon, Portugal	Portugal	x	x						
10	Ghent University, Radiobiology Research Unit, Gent, Belgium	Belgium	x	x						
11	ENEA Casaccia Research Centre, Rome, Italy	Italy	x	x						
12	Universidad de Sevilla, Departamento de Biología Celular, Sevilla, Spain	Spain	x	x						
13	Serbian Institute of Occupational Health, Belgrade, Serbia	Serbia	x	x						
14	University of Defense, Faculty of Military Health Sciences, Hradec Králové, Czech Republic	Czech Republic	x	x						
15	Genevolution, Porcheville, France	France	x	x						
16	Health Canada, Ottawa, Canada	Canada	x	x						
17	Hospital General Universitario Gregorio Marañón, Laboratorio de dosimetría biológica, Madrid, Spain	Spain	x		x					
18	Universitat Autònoma de Barcelona, Barcelona, Spain	Spain	x		x					
19	National Centre for Scientific Research ''Demokritos'', Health Physics, Radiobiology & Cytogenetics Laboratory, Agia Paraskevi, Greece	Greece	x			x				
20	Servicio de Protección Radiológica, Laboratorio de Dosimetría Biológica, Valencia, Spain	Spain	x							
21	Institut de Recherche Biomédicale des Armées (IRBA), Bretigny Sur Orge, France	France	x							
22	Laboratori Nazionali di Legnaro - Istituto Nazionale di Fisica Nucleare, Legnaro, Italy	Italy	x							
23	Radiation protection centre, Vilnius, Lithuania	Lithuania	x							
24	Nükleer Arş Ens. Türkey	Türkey	x							
25	CEA-Saclay, Gif-sur-Yvette Cedex, France	France	x							
26	Cytogenetic Biodosimetry Laboratory, Oak Ridge Institute for Science and Education, Oak Ridge, USA	USA	x							
27	Radiation Cytogenetics Laboratory, S.P. Grigoriev Institute for Medical Radiology and Oncology of Ukrainian National Academy of Medical Science, Kharkiv, Ukraine	Ukraine	x							

Continued on next page

TABLE 2
Continued.

No.	Institution	Nation (n = 27)	Biological dosimetry						Physical dosimetry		
			Cytogenetic assays				Molecular Biology				
			DCA	CBMN	FISH	PCC	gH2AX	GE	EPR	LUM	
28	Columbia University, Center for Radiological Research, New York, United States	USA		x				x			
29	Stockholm University, MBW Department, Stockholm, Sweden	Sweden			x			x			
30	Forschungszentrum Jülich, Jülich, Germany	Germany						x			
31	University of Arizona, Center for Applied Nanobioscience & Medicine, Phoenix, United States	USA						x			
32	Radiation Dosimetry Lab, Stillwater, United States	USA							x	x	
33	Ruđer Bošković Institute, Division of Physical Chemistry, Zagreb, Croatia	Croatia							x	x	
34	Università Degli Studi di Palermo, Dipartimento di Fisica e Chimica, Palermo, Italy	Italy							x		
35	Naval Dosimetry Center, Bethesda, United States	USA							x		
36	Medical University of Gdansk, Department of Physics and Biophysics, Gdansk, Poland	Poland							x		
37	Belgian Nuclear Research Center SCK CEN, Mol, Belgium	Belgium								x	
38	Paris Lodron University of Salzburg, Salzburg, Austria	Austria								x	
39	Academy of Sciences, Institute of Nuclear Physics, Krakow, Poland	Poland								x	
40	National Institute of Public Health, Radiation Hygiene Laboratory, Bucharest, Romania	Romania								x	
Examinations on prepared slides or images from other teams only											
41	Department of Risk Analysis and Biodosimetry Institute of Radiation Emergency Medicine, Hirosaki University 66-1 Hon-cho, Hirosaki, Aomori 036-8564, Japan	Japan	x								
42	Department of Radiation Life Sciences, Fukushima Medical University School of Medicine 1 Hikariga-oka, Fukushima City 960-1295, JAPAN	Japan	x								
43	Department of Radiation Biology and Protection, Atomic Bomb Disease Institute, Nagasaki University 1-12-4 Sakamoto, Nagasaki, 852-8523, Japan	Japan	x								
44	National Institutes for Quantum and Radiological Science and Technology, National Institute of Radiological Sciences, Chiba, Japan	Japan	x		x						
45	Dalat Nuclear Research Institute, Radiation Technlogy & Biotechnology Center, Dalat City, Vietnam	Vietnam	x	x							
46	Singapore Nuclear Research and Safety Initiative (SNRSI)	Singapore	x								
		Sum	**33**	**16**/14	**7**	**3**/2	**6**	**8**	**6**/5	**7**	$\sum$ = **86**/82
	No. dose estimates/assay		**108**	**63**	**21**	**9**	**24**	**105**	**51**	**67**	$\sum$ = **448**

Notes. The number of teams per assay and the number of dose estimates per assays are provided in the lower part of the table. Numbers after the slash (gray) refer to the number of teams and dose estimates, which were finally eligible for analysis. Abbreviations: dicentric chromosome assay [DCA], cytokinesis-block micronucleus assay [CBMN], stable chromosomal translocation assay [FISH] assays, premature chromosome condensation assay [PCC], gamma-H2AX foci [gH2AX], gene expression assays [GE], electron paramagnetic resonance [EPR] and optically or thermally stimulated luminescence [LUM].

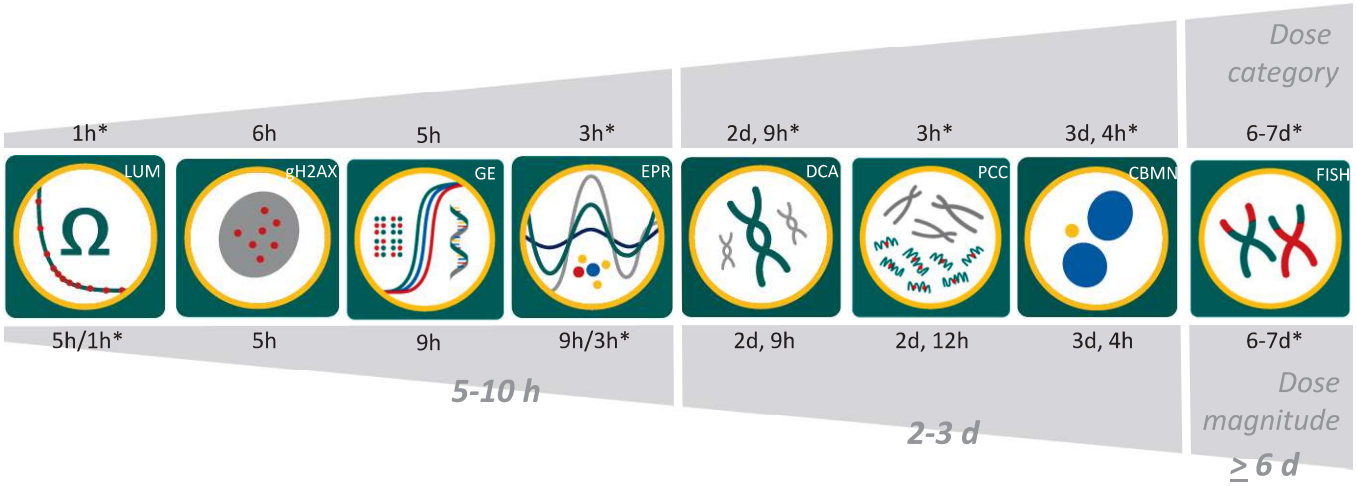

FIG. 2. The earliest report times of dose categories (low, medium, high; upper part), as well as dose estimates (dose magnitude; lower part), are provided for all assays. Three categories in report time were defined and are expressed in bold gray letters. Asterisks refer to suspected dose estimates and are not actual reported dose estimates. Assays are ordered over report time of dose estimates. Abbreviations: optically or thermally stimulated luminescence [LUM], gamma-H2AX foci [gH2AX], gene expression assays [GE], electron paramagnetic resonance [EPR], dicentric chromosome assay [DCA], premature chromosome condensation assay [PCC], cytokinesis-block micronucleus assay [CBMN] and stable chromosomal translocation assay [FISH] assays.

the statistical analysis. One EPR team published their EPR enamel data in another journal so that these data had to be excluded from this publication. Also, several teams experienced difficulties in e.g., lymphocyte stimulation for the cytogenetic assays. All of this reduced the number of contributing teams for EPR (n = 5), CBMN (n = 14) and PCC (n = 2). Overall, 82 teams successfully reported dose estimates (Table 2). Teams were permitted to provide crude early dose estimates and later more precise evaluations [but within the given 6-week report time interval for dose estimates (Supplementary[1] Table S1; https://doi.org/10.1667/RADE-22-00207.1.S1)]. Different materials were irradiated (EPR and LUM) and different GE assays employed, resulting in more than one dose estimate from some teams and a total of 554 dose reports overall.

For further analysis, these 554 dose reports were reduced to 445 for reasons as shown above and by applying the following rules to eliminate redundancy (Supplementary Table S1; https://doi.org/10.1667/RADE-22-00207.1.S1). For instance, the number of reported dose estimates for established assays (DCA and CBMN) was restricted to one per team according to the following rules: 1. Results from several scorers per team were combined into a single dose estimate; 2. Only Biodose Tools results were used if results were provided based on several different software tools (*65*); 3. Dose estimates generated from X-ray calibration curves were used if results were provided based on both X-ray and γ-ray curves.

Due to the exploratory nature of the GE assay and to deduce the optimal gene or gene combination, all contributions were accepted for further analysis. Finally, 445 dose estimates from 82 teams were thus eligible for analysis.

Delivery and Reporting Time of Dose Estimates

Delivery times of irradiated materials were 20–24 h for most countries within the EU (e.g., Sweden, UK, France, Spain, Poland and Czech Republic) and 25–45 h for North America (e.g., 33 h for New York or Phoenix, AZ) as well as Korea (42 h). Delivery times of more than 48 h were recorded for some destinations in North America, such as Oak Ridge, TN (50 h), Stillwater, OK (52 h and 147 h), Ottawa, Canada (51 h) or Eastern/Central European countries such as, e.g., Belgrade, Serbia (68 h), Zagreb, Croatia (76 h), or Gdansk, Poland (141 h). Transit time for one package to Kharkov, Ukraine was 30 days.

Participants were asked to report preliminary dose estimations in categories (lowest, medium, highest exposure), which applied more to the physical and molecular biological assays, as well as providing final dose estimates in Gy. Under the prerequisite that teams should perform this task with high priority where possible, the earliest report times were documented per assay (Fig. 2). LUM, GE, gH2AX and EPR provided dose estimates within 5–10 h and several teams calculated those results within 1–3 h under optimal conditions (see asterisks in Fig. 2). The earliest DCA and PCC dose reports arrived at 2.5 days and the earliest CBMN dose reports required about 3 days. Categorical dose estimation of three blinded coded samples within 3 h was assumed and not reported for the PCC assay under optimal conditions. FISH dose estimates were not performed with high priority by the teams involved and thus these arrived weeks after delivery of the blinded coded

[1] Editor's note. The online version of this article (DOI: https://doi.org/10.1667/RADE-22-00207.1) contains supplementary information that is available to all authorized users.

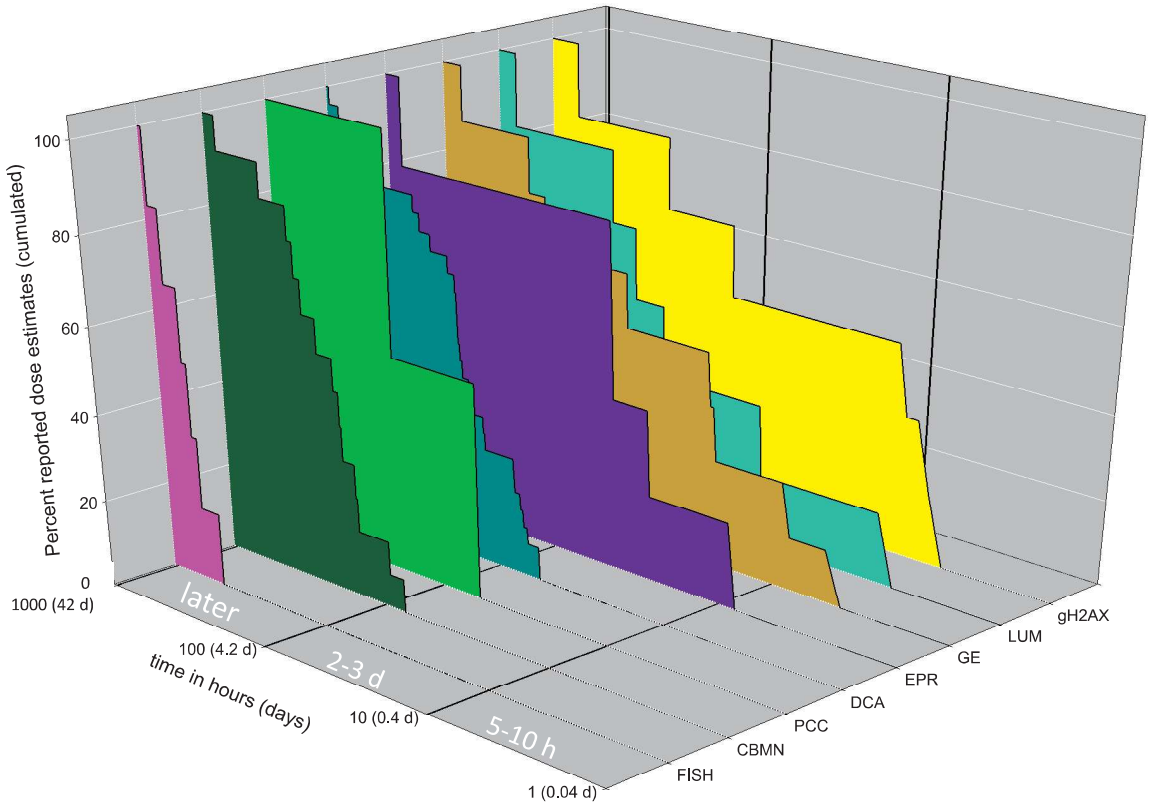

FIG. 3. Reporting times of dose estimates/categories cumulated (in percent) over time are depicted for all assays. Three categories in report time were defined and expressed in white letters (left side of the graph). Assays are ordered over report time of dose estimates. Abbreviations: gamma-H2AX foci [gH2AX], optically or thermally stimulated luminescence [LUM], gene expression assays [GE], electron paramagnetic resonance [EPR], dicentric chromosome assay [DCA], premature chromosome condensation assay [PCC], cytokinesis-block micronucleus assay [CBMN] and stable chromosomal translocation assay [FISH] assays.

samples. The teams assumed the earliest reports could be delivered around a week after the arrival of samples at their laboratory under optimal conditions. Since most teams could not or chose not to perform the assays with high priority, dose estimates arrived at later time points over the whole 6-week period provided for dose reports (Fig. 3).

Allocation of Reported Dose Estimates to Clinically Relevant Groups

Most assays and teams correctly allocated the unexposed reference sample to the 0–1 Gy dose band, representing the group of unexposed or lower exposed individuals including a range of 85–100% (Table 3). Misclassifications of the unexposed samples as representing the group of medium exposed individuals (1–2 Gy dose interval) were reported by the FISH assays (14.3%), EPR (6.3%) and CBMN (4.8%; Table 3) and GE (3.2%). Moreover, for all assays, none of the irradiated samples (>0 Gy) were estimated as exactly 0 Gy and of the sham-irradiated samples, 77.1% were estimated as exactly 0 Gy (Supplementary Table S1; https://doi.org/10.1667/RADE-22-00207.1.S1).

The medium exposed reference sample (1.2 Gy) was correctly allocated to the medium exposed group (1–2 Gy dose band) in 50–100% of reported dose estimates by most assays. However, reported dose estimates of GE (29%) and gH2AX (50%) falsely indicated an unexposed-low exposed group and 14–50% of other assays reported dose estimates falsely allocating the highly exposed group (Table 3). Only for the PCC assay both reported dose estimates correctly allocated these samples to the medium exposed group.

The highly (3.5 Gy) exposed reference sample was correctly allocated to the highly exposed group (>2 Gy) in 100% by most assays, 89.3% by GE assays and 66.7% by gH2AX assays, which falsely allocated the highly-exposed sample to the unexposed-low exposure group in 33.3% (Table 3). Also, all reported doses that were estimated as >3.5 Gy were from samples exposed to the highest dose (3.5 Gy), except for EPR examination of tooth enamel and GE dose estimates of one team (Supplementary Table S1; https://doi.org/10.1667/RADE-22-00207.1.S1).

Taken together, the reported dose estimates correctly allocated the clinically relevant group of unexposed or highly exposed individuals in 90–100% of cases, except regarding tooth enamel by EPR (reported as kerma in enamel and not kerma in air/water as done by other materials, but when converted into the proper quantity, i.e., to kerma in air, expected dose estimates could be recalculated in most cases) and FISH assays for the

TABLE 3
Overview on Reported Dose Estimates for the Unexposed (0 Gy), Low Exposed (1.2 Gy) and Highly Exposed (3.5 Gy) Reference Samples and Their Allocation to Dose Bands Referring to Clinically Relevant Groups

	Reference dose								
	0 Gy			1.2 Gy			3.5 Gy		
	Reported dose estimates allocated to dose categories of clinical relevance								
Assay	0–1 Gy	>1–2 Gy	>2 Gy	0–1 Gy	>1–2 Gy	>2 Gy	0–1 Gy	>1–2 Gy	>2 Gy
EPR									
Freq	15	1	0	3	9	3	0	0	13
Percent	93.8	6.3	0.0	20.0	60.0	20.0	0.0	0.0	100.0
LUM									
Freq	23	0	0	4	14	3	0	0	21
Percent	100.0	0.0	0.0	19.0	66.7	14.3	0.0	0.0	100.0
DCA									
Freq	36	0	0	2	26	8	0	0	36
Percent	100.0	0.0	0.0	5.6	72.2	22.2	0.0	0.0	100.0
CBMN									
Freq	20	1	0	2	15	4	0	0	21
Percent	95.2	4.8	0.0	9.5	71.4	19.0	0.0	0.0	100.0
FISH									
Freq	6	1	0	0	4	3	0	0	7
Percent	85.7	14.3	0.0	0.0	57.1	42.9	0.0	0.0	100.0
PCC									
Freq	2	0	0	0	2	0	0	0	2
Percent	100.00	0.00	0.00	0.0	100.0	0.0	0.0	0.0	100.0
GE									
Freq	30	1	0	9	7	15	1	2	25
Percent	96.8	3.2	0.0	29.0	22.6	48.4	3.6	7.1	89.3
gH2AX									
Freq	6	0	0	3	3	0	2	0	4
Percent	100.0	0.0	0.0	50.0	50.0	0.0	33.33	0.00	66.67

Note. The number of dose estimates (semiquantitative data are excluded) is provided as a frequency and in percent for each assay.

unexposed/-low exposed as well as the gH2AX assay for the highly exposed group.

Inter-Assay Comparison Based on AD and Corresponding Uncertainty Dose Interval

To compare the assays in terms of the absolute difference to the reference dose the 25% (lower quartile), 50% (median) and 75% (upper quartile) quantiles were used (Table 4). The lower quartile shows the highest AD for the 25% of the teams that were closest to the reference dose, the median shows the AD were 50% of the teams had higher/lower ADs and the upper quartile shows the lowest AD for the 25% of the teams that were farthest from the reference dose.

The 0 Gy sham-irradiated samples were reported as 0 Gy by most of the teams for all assays employed (Fig. 4A), resulting in median ADs of 0 Gy for all assays (Fig. 4B; Table 4), suggesting that at least 50% of the teams for each assay correctly identified the control sample. Upper quartile ADs of 0.1-0.2 Gy were within the uncertainty dose interval, but reported maximum ADs of >1 Gy for EPR, CBMN, FISH and GE revealed some considerable outliers (Table 4). For EPR (6.2%), CBMN (4.6%), FISH (14.3%), GE (6.5%) and DCA (5.6%) approximately 5–14% of the reported dose estimates were outside the ±0.5 Gy interval (Fig. 4).

Regarding the blinded coded sample #2 (1.2 Gy), lower quartiles of ADs ranging between 0–0.4 Gy showed that the 25% of the reported dose estimates closest to the reference dose were still in the ±0.5 Gy triage uncertainty dose interval for all of the assays and minimal ADs of 0 to 0.2 Gy indicated a close agreement of reported relative to reference dose estimates by best performing teams (Table 4 and Fig. 4C and D). However, GE (0.9 Gy) and FISH (0.7 Gy) had relatively high median ADs and GE (3.8 Gy), EPR (1.1 Gy) and FISH (1 Gy) had relatively high upper quartiles of the ADs, which implied that several of the reported dose estimates showed a considerable deviation from the reference dose. For blinded coded sample #2 between 29% (GE) and 76.2% (CBMN) of the reported dose estimates were within the ±0.5 Gy interval with the other assays ranging in between (Fig. 4C). For GE and EPR some of the reported dose estimates showed substantial overestimation (up to sixfold) of the reference dose (Fig. 4; Table 4). For GE, these outliers were all caused by dose estimates reported by the same team and for EPR the observed outliers were all based on dose estimates from tooth enamel. In addition, some labs also underestimated the reference

TABLE 4
Descriptive Statistics of Absolute Differences (AD) Calculated between Reported Dose Estimates and Reference Doses

	Absolute difference (Gy)							
Parameter	EPR	LUM	DCA	CBMN	PCC	FISH	gH2AX	GE
Sample 1 (0 Gy)								
n	16	22	36	21	2	7	6	31
mean	0.1	0.0	0.0	0.1	0.1	0.3	0.0	0.1
min	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
max	1.2	0.2	0.7	1.6	0.2	1.9	0	1.2
Quantiles								
75%	0.1	0.0	0.0	0.0	0.2	0.2	0	0.0
Median	0.0	0.0	0.0	0.0	0.1	0.0	0	0.0
25%	0.0	0.0	0.0	0.0	0.0	0.0	0	0.0
Sample 2 (1.2 Gy)								
n	15	21	36	21	2	7	6	31
mean	1.0	0.4	0.51	0.4	0.3	0.8	0.4	1.8
min	0.0	0.0	0.0	0.1	0.0	0.0	0.2	0.0
max	6,1	2,2	1,4	0,96	0,6	2,2	0,8	6,4
Quantiles								
75%	1,1	0,6	0,7	0,5	0,6	1.00	0,5	3,8
Median	0,3	0,2	0,5	0,4	0,3	0.70	0,4	0,9
25%	0,1	0,1	0,3	0,3	0	0.20	0,2	0,4
Sample 3 (3.5 Gy)								
n	13	21	36	21	2	7	6	28
mean	2.8	0.8	0.9	0.7	0.7	1.6	1.8	2.7
min	0.0	0.0	0.0	0.0	0.5	0.1	0.2	0.1
max	16.00	4.70	2.00	1.80	0.80	5.90	3.3	8.80
Quantiles								
75%	0.90	0.60	1.40	0.77	0.80	2.10	3.1	4.20
Median	0.40	0.40	1.00	0.50	0.65	1.10	1.5	1.85
25%	0.30	0.10	0.45	0.30	0.50	0.30	1.3	0.75

Note. Quantiles were calculated using SAS and are shown for 0 Gy (upper part), 1.2 Gy (middle part) and 3.5 Gy irradiated samples (lower part).

dose by more than 0.5 Gy for gH2AX (33%) and GE (16%). In contrast, for the remaining, and in particular for the cytogenetic assays, all reported dose estimates outside the ±0.5 Gy interval overestimated the reference dose (Fig. 4C).

For blinded coded sample #3 (3.5 Gy), the lower quartiles ranged between 0.1 and 0.5 Gy for all assays besides gH2AX (1.3 Gy) and GE (0.75 Gy; Table 4; Fig. 4E and F), suggesting that even the best 25% of the reported dose estimates showed a relatively high deviation for this assay. Minimal ADs of 0 to 0.2 Gy for all except PCC assays (0.5 Gy) indicated a close agreement of reported relative to reference dose estimates by best performing teams. The median ADs were approximately 1 Gy for DCA (1 Gy), FISH (1.1 Gy) and higher for gH2AX (1.5 Gy) and GE (1.85 Gy; Table 4). Hence, more than 50% of the dose estimates were >1 Gy for these assays. The upper quartile was >1 Gy for half of the assays (DCA, 1.4 Gy; FISH, 2.1 Gy; gH2AX, 3.1 Gy; GE, 4.2 Gy) and lower 1 Gy for EPR (0.9 Gy), LUM (0.6 Gy), CBMN (0.77 Gy) and PCC (0.8 Gy) assays, suggesting that at least 25% of the labs showed a deviation > 1 Gy for most of the assays. In addition, maximum ADs of > 3 Gy for EPR (16.0 Gy), GE (8.8 Gy), FISH (5.9 Gy), LUM (4.7 Gy), and gH2AX (3.3 Gy) revealed considerable deviations (up to 4.6-fold) for some of the reported dose estimates (Table 4 and Fig. 4E and F).

Accuracy of the reported dose estimates within ±1 Gy of the 3.5 Gy reference dose ranged among all assays between 17% (gH2AX) and 100% (PCC) (Fig. 4E). For gH2AX all 83.3% of the reported dose estimates outside the ±1 Gy interval demonstrated underestimation over all teams involved. For GE 14.3% underestimated the reference dose (Fig. 4E). Similar to the 1.2 Gy irradiated blinded coded sample, some of the reported dose estimates for EPR and GE strongly overestimated the reference dose. These dose estimates were again all based on tooth enamel for EPR and were from only one team for GE. However, when recalculating EPR tooth enamel data by introducing the correction factor for conversion of kerma in enamel to kerma in air, all recalculated dose estimates from three out of four teams revealed dose estimates within the accepted uncertainty interval for dose estimation of all three reference samples (Table 5).

DISCUSSION

The threat of large-scale radiological or nuclear scenarios requires exercises and inter-comparisons to improve preparedness (*66*). Along this line RENEB continues to

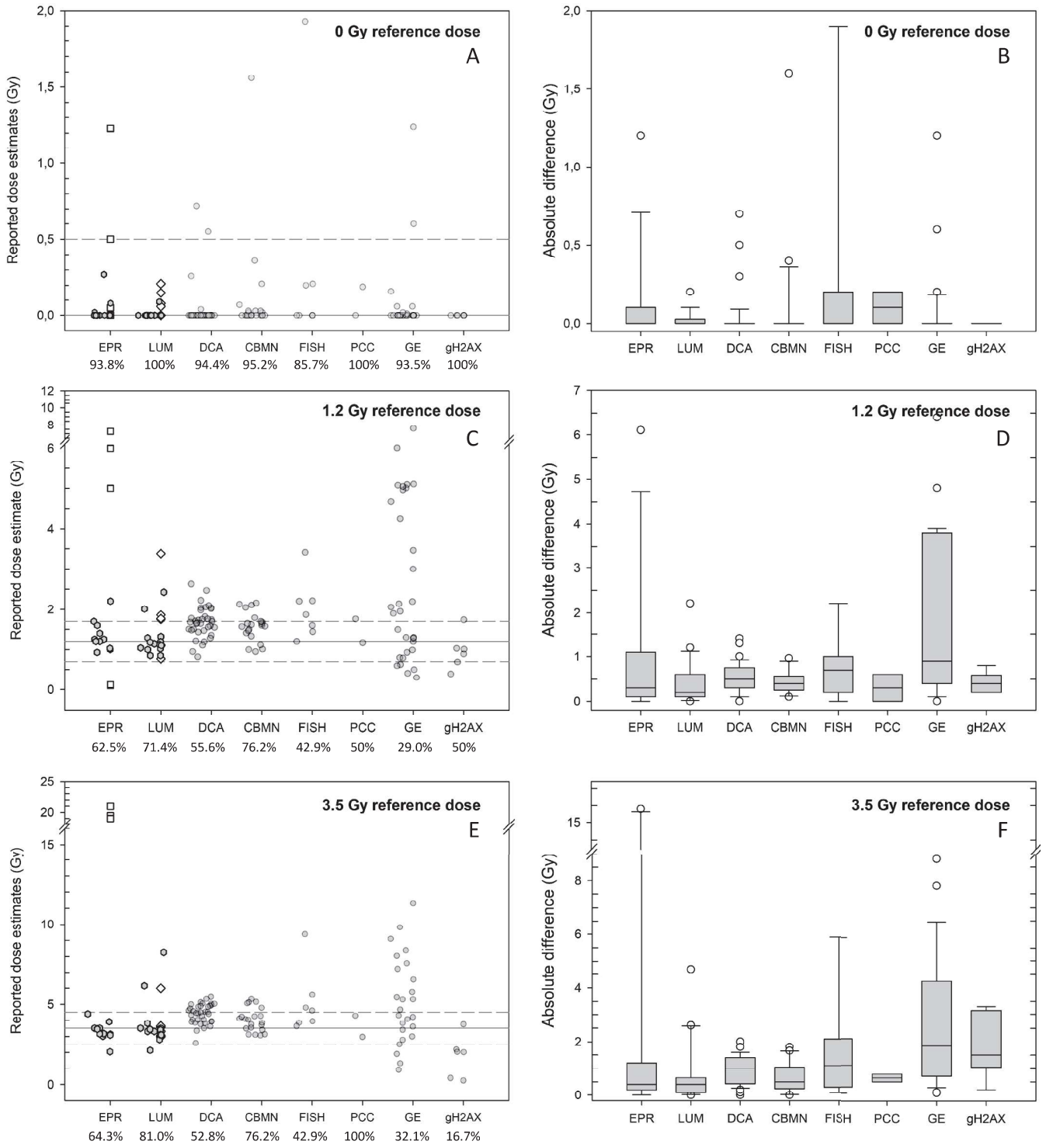

FIG. 4. Distribution of reported dose estimates (jitter plots to the left) and calculated absolute differences (box plots to the right) are shown for each team and assay regarding the 0 Gy irradiated samples (panels A andB), 1.2 Gy irradiated sample (panels C and D) and 3.5 Gy irradiated samples (panel E and F). Short-dashed horizontal lines refer to the corresponding uncertainty interval as recommended for triage dosimetry and percentages shown below the assay labels (x-scale) refer to the number of reported dose estimates lying within these dose intervals. Another horizontal solid line visualizes reference doses. EPR and LUM (comprising optically and thermally stimulated luminescence assays, OSL, TL) reported dose estimates refer to kerma in air except for enamel (white squares), which is kerma in enamel and cannot be compared with kerma in air reference dose estimates, but have been reported as that and are therefore shown. Resistor based dose estimates employing LUM (OSL) are shown as white-filled diamonds on the right side of the LUM data. All other inorganic based (e.g., glass) EPR and OSL reported dose estimates are depicted as transparent gray hexagons and TL results are depicted as translucent black hexagons on the left side of the LUM data. Reported and reference dose estimates regarding cytogenetic and molecular biological assays refer to kerma in water, respectively. Corresponding gray circles refer to irradiated blood samples. The conversion factor (Table 1) is 1.08 from kerma in air to kerma in water.

TABLE 5
The Table Provides Teams' Reported Kerma in Tooth Enamel for all Three Reference Samples and the Corresponding Recalculated Kerma in Air as Outlined in the Material and Method Section

	Test samples					
	0 Gy		1.2 Gy		3.5 Gy	
Team ID	reported	re-calculated	reported	re-calculated	reported	re-calculated
1	0.05	0.01	0.1	0.02	>1.5	>0.23
	0	0.00	0.12	0.02	>1.5	>0.23
2	1.23	0.19	7.26	1.12	19.45	2.99
3	0.00	0.00	5.50	0.85	18-22	2.8-3.4
4	0.50	0.08	5.00	0.77	19.00	2.92

Note. Team 1 provided two estimates per reference samples and all other teams one.

run exercises to sustain laboratory skills for providing dose estimations that support medical management decision making, including both biodosimetry and physical dosimetry exercises (*14, 37–46, 61, 62, 67–69*). These exercises comprise other tasks as well, namely, ascertaining the actual status of preparedness in different laboratories across the globe, facilitating the development of emerging technologies for dosimetry purposes and working together as a community. These scenarios demand a concerted action of the small number of radiobiological and physical dosimetry laboratories currently existing worldwide. In 2021 laboratories of the RENEB network were invited to participate in a quality controlled ILC. Via different channels (e.g., WHO newsletter) a number of teams outside the RENEB community requested participation in the ILC. In the RENEB ILC 2021, 86 teams from 27 nations spanning three continents worked together and provided 554 dose estimates. The exclusion of for example redundancies resulted finally in 445 dose estimates used for analysis. These numbers reflect the requirement and recognition for exercises to gain and maintain preparedness. Within the RENEB ILC 2021, established cytogenetic (DCA, CBMN, FISH, PCC) and emerging biological dosimetry assays (gH2AX, GE), as well as physical dosimetry-based assays (EPR, LUM), were run in parallel to determine and compare the dose-assessment quality. Exposure estimates are important to support medical management decision-making (*2*) , which is the primary task of RENEB in emergency situations. From the clinical point of view, groups of unexposed to lower exposed, moderate exposed (no severe acute health effects expected) and highly exposed individuals requiring early intensive medical health care need to be identified and discriminated (*5, 6, 8*). Blinded coded irradiated samples exposed to 0, 1.2 and 3.5 Gy approximately corresponding to these clinically relevant groups, were distributed during the RENEB ILC 2021. We first, examined the allocation of reported dose estimates to corresponding clinically relevant groups by each assay, second, calculated the number of dose estimates considering dose uncertainty intervals as recommended for triage dosimetry, and third determined the exposure accuracy by comparing the AD of reported doses relative to reference doses.

Within this exercise, the teams were asked to provide dose estimates as soon as possible since timely exposure estimates facilitate medical management decision-making (*70, 71*). Few teams were able to perform the assays with highest priority due to daily duties and coronavirus-related strict minimum staffing rules, but the earliest dose estimates/categories were reported within 5–10 h for GE, gH2AX, LUM and EPR and within 2–3 days for DCA and CBMN. Results of the FISH assay were projected to be available within 6–7 days, but this could not be confirmed, since teams could not perform this assay with the highest priority (Fig. 2). Hypothetically, reporting times within 1–3 h were assumed under optimal conditions by LUM, EPR and PCC teams (Fig. 2). However, the actual reports of most such assay teams arrived weeks after receipt of blinded coded samples (Fig. 3). These reporting time values are in good agreement with previous work regarding GE, gH2AX, DCA and CBMN (*72*) and physical and FISH assays results generated on the same sample set complete the picture. In a real case scenario, priorities in the laboratories will certainly shift, but the earliest dose estimates will be expected in the time range as outlined here. It is noteworthy that several assays do have the capacity for large-scale multiplexing (dozens or hundreds of samples are processed simultaneously). For instance, GE teams in previous exercises required about the same time (7–8 h) for an early report of 10 dose estimates (*73*) as reported for three dose estimates in this exercise, attributed to their specific workflow allowing for multiplexing. Recently, several teams demonstrated high-throughput capabilities of GE assays (*26, 74*). Within 30 h, one thousand blood samples could be processed and dose estimations, as well as clinically relevant categories, were reported with an accuracy ranging between 90–97% (*26*). Building a network and distributing the workload for cytogenetic analysis is another approach to deal with overwhelming numbers of exposed and potentially exposed individuals. In this context, problems with sample collection (*75*), the delivery of samples (see above) and the delivery time itself ranging between 1–2 days for most but not all countries, must be considered. However,

dose assessment within the first 1–3 days after exposure are required for early medical management support (*70, 71*). Hence, regional networks and knowledge of neighboring partner institution's capabilities might represent one practical solution to split cytogenetic workload. Since sample transport may be critical to guarantee fast assay performance, the access to infrastructures other than commercial carriers, e.g., to military, or civilian emergency transport capabilities must be considered as a further option to accelerate the transport procedure. Considering the current experiences, the training in logistical challenges has to become a further option for future RENEB ILC exercises.

The accuracy of the reported dose estimates expressed as absolute difference (AD) and considering accepted uncertainty dose intervals for triage biodosimetry (*25*) has herein provided promising results from all assays regarding the 0 Gy sham-irradiated samples (median AD was 0–0.1 Gy throughout, Fig. 4A and B). However, regarding the 1.2 Gy (Fig. 4 C, D) and 3.5 Gy reference samples (Fig. 4E and F), reported dose estimates exceeding the reference doses 2–6-fold were observed for EPR [if not converted to the proper quantity, i.e., to kerma in air (Table 5)], FISH and GE assays (Table 4). These extreme dose estimates were derived from only one material examined (tooth enamel for EPR assay, reported as kerma in enamel and not kerma in air/water as done by other materials, thus making comparisons impossible), the level of experience by the teams (FISH) and methodological uncertainties (GE). Also, at higher doses (1.2 Gy and 3.5 Gy), a systematic shift towards higher dose estimates by cytogenetic-based assays was observed. Detailed discussions of these unexpected results and possible reasons are presented in the following series of manuscripts, each focusing on one assay (*47–51*). Furthermore, for GE and gH2AX assays, another fraction of dose estimates lying below or above the accepted uncertainty dose interval was reported by most teams (Fig. 4C and E). This pattern remained when comparing 25% quantile ADs among teams and assays and was expected, because the free access for participating in the RENEB ILC 2021 exercise resulted in different levels of experience of teams involved in these assays. Hence, the observed performance differences among assays at the 25% quantile (representative of teams with high performance) reflect an inherent limitation of GE and gH2AX assays, especially in the dose estimations at higher doses and agree with previously cited work (*72, 73*).

The observed systematic shift of reported dose estimates for cytogenetic assays was unexpected and not seen to this extent in any of the previous ILCs conducted by RENEB or NATO exercise (*76*). This shift raised a discussion concerning the performance of radiation set up and influence of calibration practices. As clearly shown in the Material and Methods section, several quality assurance activities were performed to ensure the best overall performance, which argues in favor of correct irradiation of the samples with an uncertainty of approximately ±4% for kerma in air. The internal dosimetry group of BfS shared calibration factors for dose in water and kerma in air for their dosemeters performed by PTW. For the TM23331 chamber these resulted in conversion factors of 1.05 and 1.07 (±4%) for radiation qualities TH140 and TH200, representing the two closest qualities to the X rays used in this ILC. For the BfS TM30010 chamber the conversion factor is about 1.09 (±4%) for Co-60. Thus, the conversion factor used in this ILC of 1.08 for the calculation of dose in water from kerma in air for the irradiation of biological samples also converges within 4%. In addition, conversion factors of >1 reduce the irradiation time and thus effectively less dose application, which may lead to an underestimation of biological assays using kerma in air calibration curves, but not to an overestimation.

The physical dosimetry assays resulted in reported dose estimates of local exposure very close to the reference dose estimates and this was true for tooth enamel as well after converting reported kerma in enamel dose into recalculated kerma in air dose (Fig. 4A, C and E; Table 5). These are promising results but highly dependent on knowledge regarding exposure details (e.g., calibration samples were requested for accurate dose estimation within this exercise and blinded coded samples had, therefore, the same exposure conditions as calibration samples). It also represents a dose estimation of local exposure conditions and is highly dependent on the irradiation scenario. For instance, using glass or resistors from mobile phones provided promising dose estimates in this exercise, but front or side irradiation of mobile phones using the same dose would result in different dose estimates. For this reason, the angle response for display glass was simulated by Monte Carlo simulations and varied experimentally in laboratory irradiations with gamma and X-ray sources (*60, 77, 78*). Possible irradiation geometries as depicted in Fig. 5 reflect expected differences between mobile phone and whole-body doses as generated employing biological assays. Recent experiments on how the phone orientation and angle impacts the dose received by the phone components indicate that the doses measured can vary significantly depending upon exposure geometry (including phone position and angle). However, in rotational irradiation symmetry, the phone doses lead to an over-estimate of the average whole-body dose by an average of ~10%, independent of the phone locations tested in this study and if confirmed in future studies, may be acceptable for triage, the authors concluded (*79*). Because lymphocytes circulate within the body for a period of approximately 24 h, biological dosimetry assays based on sampling blood after an exposure can be assumed to some extent integrate different irradiation geometries and provide a mean whole-body exposure. Hence, physical and biological assays provide different dose information, which has to be considered. Interpretation of physical doses and their relationship to internal organ doses, and under what circumstances they may be representative of whole-body

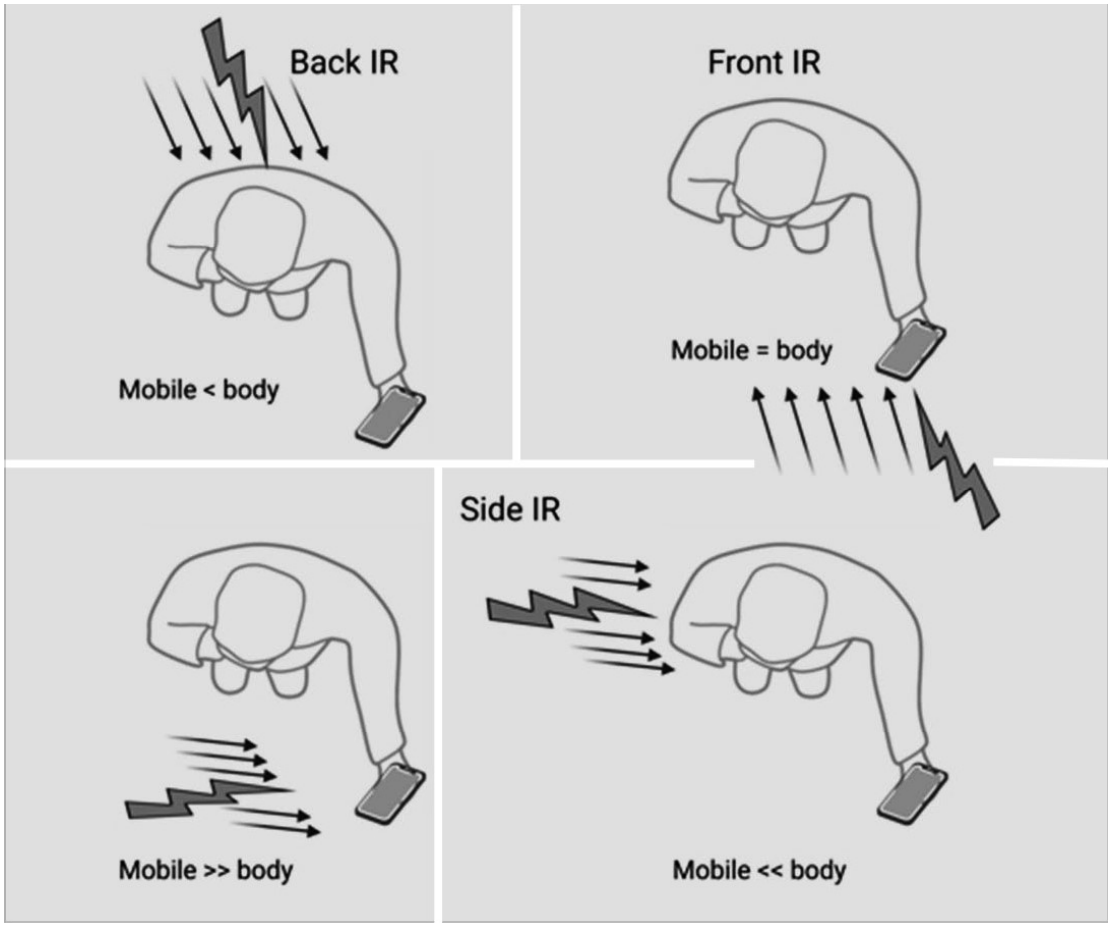

FIG. 5. This cartoon reflects different radiation exposure geometries and corresponding assumed discrepancies between physical dose estimates based on mobile phone irradiation and mean whole-body dose as measured with biological dosimetry assays. Abbreviations: IR, irradiation; ''mobile < body'' refer to exposure differences (<, >, =) measured in mobile phones and the whole body depending on different exposure geometries.

dose, are subjects of current extensive research (*80–82*). The issue is very complex and depends critically on the locations of the physical dosimetry material (e.g., phones) on the body and the orientation of the body with respect to the incident radiation field, as well as the quality of the radiation field. Although physical dosimetry and biodosimetry measurements performed well in this inter-comparison, more detailed studies with anthropomorphic phantoms and multiple irradiation scenarios in realistic conditions are required before conclusions can be made on the comparisons between physical dosimetry and biodosimetry in realistic emergency dosimetry situations. Some experiments of this type are currently underway within the EURADOS and RENEB community. However, both methods support our search for a meaningful association between exposure, dose, and acute health effects. Ideally, the best possible exposure data can be collected when the various assays are applied in a concerted way to accurately respond to different exposure scenarios, as suggested by others already (*52*).

From the dosimetry point of view and for long-term epidemiological follow-up with the focus on chronic health effects, it is desirable to estimate doses as accurately as possible. From the clinical point of view regarding acute health effects, dose ranges often provide sufficient information to address urgent clinical or diagnostic needs (*6, 8*). For this reason, in this study, the samples were irradiated with clinical-relevant doses and examined for dose categories as already described. For all assays, only sham-irradiated samples were identified as unexposed (exactly 0 Gy) and all doses estimated as $\geq$3.5 Gy were from samples irradiated with the highest dose of 3.5 Gy (excluding EPR tooth enamel kerma in enamel dose estimates and GE measurements of one team), suggesting that those samples reported with doses of exactly 0 Gy or $\geq$3.5 Gy were truly unexposed or highly exposed (Supplementary Table S1; https://doi.org/10.1667/RADE-22-00207.1.S1). This could be also shown for most of the recalculated EPR tooth enamel kerma in air dose estimates (Table 5) and a recent publication associated to the RENEB ILC 2021 (*83*) Furthermore, reported dose estimates correctly allocated clinically relevant groups of unexposed-low individuals in 94–100% of cases, with the exception of the FISH assay

(86%). For highly exposed samples the assays performed successfully (100%) with the exception of GE (89%) and gH2AX assays (67%; Table 3). These are promising results to supplement medical care management of acute health effects. However, it must be noted that highly exposed (3.5 Gy) reference samples were systematically categorized towards unexposed-to-low exposed individuals not requiring hospitalization and immediate clinical care when using the gH2AX assay (Table 4). This reflects a limitation of the gH2AX assay to reveal DSB-equivalent foci numbers shortly after acute high-dose photon irradiation when more than 1 DSB is contained in individual foci (*84*) or the gH2AX signals converge to result in a confluent signal pattern (*85*).

Conversely, lower (1.2 Gy) exposed reference samples not requiring immediate care are systematically estimated towards the lower and highly exposed group by all assays, where immediate clinical care would be considered (Table 3). This was partly caused by methodological issues and will be further discussed in a series of publications with focus on each assay within this special issue (*47–51*). Hence, the application of each of these assays requires a deep understanding of the advantages and limitations in the different exposure circumstances.

This exercise provided additional experiences covered under ''lessons learned''. These included that sample delivery via courier requires the urgent need to prior-to-shipment contacting the local office of the courier for assistance and guidance with transport regulations. Sending packages in advance of an exercise would further smoothen this challenging procedure. Only two out of 86 teams could not generate results, because of difficulties in processing cytogenetic samples. Temperature loggers and TLD chips sent together with the samples indicated no deviations from the norm. Other laboratories indicated difficulties with lymphocyte stimulation of the healthy young donor's blood and missing results might be attributable to that. Delays in reporting dose estimates were certainly caused by coronavirus-related strict minimum staffing rules when performing assays and other priorities to fulfill the daily workload. In addition, the coronavirus pandemic caused difficulties in laboratory use and further delays in reporting dose estimates. Furthermore, it appeared that reporting dose estimates by using the agreed sample code is a prerequisite for the success for every exercise. Providing each laboratory's code instead (occurring in a few cases) generates uninformative results, because dose estimates cannot be assigned correctly. Participants must be informed about this repeatedly. Although documented for this exercise, DCA assay repair time was not conducted at 37°C, but at room temperature (currently examined as one potential source of observed overestimation by cytogenetic assays). Another round of discussion with team members ahead of the exercise is indicated to avoid this kind of mistakes. Irradiation at 37°C and not at room temperature would provide another improvement for the next exercise.

There are a number of limitations for the exposure scenario used in this exercise. We deliberately restricted all measurements to blood samples taken from only one individual to focus on methodological variance and to exclude inter-individual variance, which has been reported for several of the biological assays (*86–88*). For the same reason, we varied only the dose and did not simulate non-uniform radiation exposures. It is important to note that results may well differ considerably if the exposures are non-uniform. Biological assays such as the DCA and the gH2AX assay have been formally shown to be able to detect and quantify non-uniform exposures in certain scenarios, based on the distribution of dicentrics or foci respectively, among analyzed cells (*89*). Even then, the small number of cells scored in triage mode for DCA may pose difficulties in the case of highly non-uniform exposures (*90*). More data and better statistical methods are needed to fully understand the impact of non-uniform exposures on biological dose estimates and associated uncertainties (*91*).

In summary, EPR and LUM assays proved their usefulness to provide localized dose information. All assays appeared comparably applicable for the identification of unexposed and highly exposed individuals and the allocation of medical relevant groups, with the latter requiring medical support for the acute radiation scenario simulated in this exercise. The cytogenetic methods DCA and CBMN as established biological methods for providing a mean whole-body exposure revealed a systematic shift in dose estimations in comparison to the reference dose. Possible reasons will be discussed in more detail in the assay specific papers (*48, 49*). Difficulties exist for the discrimination of moderately and highly exposed individuals. It is noteworthy that, even a large-scale exercise such as this one could be successfully organized using only emails and a few online information sessions. The ILC clearly demonstrates the need to conduct regular exercises to identify research needs but also to identify technical problems and to optimize future ILCs.

SUPPLEMENTARY MATERIAL

Table S1. Overview of unfiltered dose estimates reported within the 6-week period provided for the exercise. Elimination of redundant dose estimates (gray) resulted in a selection of dose estimates (black) finally eligible for analysis.

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REFERENCES

1. Waselenko JK, MacVittie TJ, Blakely WF, Pesik N, Wiley AL, Dickerson WE, et al. Medical management of the acute radiation syndrome: recommendations of the Strategic National Stockpile Radiation Working Group. Ann Intern Med. 2004; 140(12):1037-51. 10.7326/0003-4819-140-12-200406150-00015.
2. Blakely WF, Port M, Abend M. Early-response multiple-parameter biodosimetry and dosimetry: risk predictions. J Radiol Prot. 2021; 41(4). 10.1088/1361-6498/ac15df.
3. Dainiak N, Albanese J, Kaushik M, Balajee AS, Romanyukha A, Sharp TJ, et al. Concepts of Operations for a Us Dosimetry and Biodosimetry Network. Radiat Prot Dosimetry. 2019; 186(1):130-8. 10.1093/rpd/ncy294.
4. O'Brien G, Cruz-Garcia L, Majewski M, Grepl J, Abend M, Port M, et al. FDXR is a biomarker of radiation exposure in vivo. Sci Rep. 2018; 8(1):684. 10.1038/s41598-017-19043-w.
5. Abend M, Port M. Contribution of Biodosimetry to Different Medical Issues. Radiat Prot Dosimetry. 2019; 186(1):123-5. 10. 1093/rpd/ncy278.
6. Port M, Herodin F, Drouet M, Valente M, Majewski M, Ostheim P, et al. Gene Expression Changes in Irradiated Baboons: A Summary and Interpretation of a Decade of Findings. Radiat Res. 2021; 195(6):501-21. 10.1667/RADE-20-00217.1.
7. Amundson SA. Transcriptomics for radiation biodosimetry: progress and challenges. Int J Radiat Biol. 2021:1-9. 10.1080/09553002.2021.1928784.
8. Port M, Majewski M, Abend M. Radiation Dose Is of Limited Clinical Usefulness in Persons with Acute Radiation Syndrome. Radiat Prot Dosimetry. 2019; 186(1):126-9. 10.1093/rpd/ncz058.
9. Bailiff IK, Sholom S, McKeever SWS. Retrospective and emergency dosimetry in response to radiological incidents and nuclear mass-casualty events: A review. Radiat Meas. 2016; 94:83-139. https://doi.org/10.1016/j.radmeas.2016.09.004.
10. Measurements ICoRUa. Methods for initial-phase assessment of individual doses following acute exposure to ionizing radiation. ICRU Report 94. SAGE Journals: ICRU-International Commission on Radiation Units and Measurements; 2019.
11. Cytogenetic Dosimetry: Applications in Preparedness for and Response to Radiation Emergencies. Vienna: International Atomic Energy Agency; 2011.
12. Di Giorgio M, Barquinero JF, Vallerga MB, Radl A, Taja MR, Seoane A, et al. Biological dosimetry intercomparison exercise: an evaluation of triage and routine mode results by robust methods. Radiat Res. 2011; 175(5):638-49. 10.1667/RR2425.1.
13. Wilkins RC, Romm H, Oestreicher U, Marro L, Yoshida MA, Suto Y, et al. Biological Dosimetry by the Triage Dicentric Chromosome Assay - Further validation of International Networking. Radiat Meas. 2011; 46(9):923-8. 10.1016/j.radmeas.2011.03.012.
14. Oestreicher U, Samaga D, Ainsbury E, Antunes AC, Baeyens A, Barrios L, et al. RENEB intercomparisons applying the conventional Dicentric Chromosome Assay (DCA). Int J Radiat Biol. 2017; 93(1):20-9. 10.1080/09553002.2016.1233370.
15. Royba E, Repin M, Pampou S, Karan C, Brenner DJ, Garty G. RABiT-II-DCA: A Fully-automated Dicentric Chromosome Assay in Multiwell Plates. Radiat Res. 2019; 192(3):311-23. 10.1667/RR15266.1.
16. Flegal FN, Devantier Y, McNamee JP, Wilkins RC. Quickscan dicentric chromosome analysis for radiation biodosimetry. Health Phys. 2010; 98(2):276-81. 10.1097/HP.0b013e3181aba9c7.
17. Flegal FN, Devantier Y, Marro L, Wilkins RC. Validation of QuickScan dicentric chromosome analysis for high throughput radiation biological dosimetry. Health Phys. 2012; 102(2):143-53. 10.1097/HP.0b013e3182307758.
18. Kulka U, Wojcik A, Di Giorgio M, Wilkins R, Suto Y, Jang S, et al. Biodosimetry and Biodosimetry Networks for Managing Radiation Emergency. Radiat Prot Dosimetry. 2018; 182(1):128-38. 10.1093/rpd/ncy137.
19. Romm H, Beinke C, Garcia O, Di Giorgio M, Gregoire E, Livingston G, et al. A New Cytogenetic Biodosimetry Image Repository for the Dicentric Assay. Radiat Prot Dosimetry. 2016; 172(1-3):192-200. 10.1093/rpd/ncw158.
20. Schunck C, Johannes T, Varga D, Lorch T, Plesch A. New developments in automated cytogenetic imaging: unattended scoring of dicentric chromosomes, micronuclei, single cell gel electrophoresis, and fluorescence signals. Cytogenet Genome Res. 2004; 104(1-4):383-9. 10.1159/000077520.
21. Vaurijoux A, Gruel G, Pouzoulet F, Gregoire E, Martin C, Roch-Lefevre S, et al. Strategy for population triage based on dicentric analysis. Radiat Res. 2009; 171(5):541-8. 10.1667/RR1664.1.
22. Gruel G, Gregoire E, Lecas S, Martin C, Roch-Lefevre S, Vaurijoux A, et al. Biological dosimetry by automated dicentric scoring in a simulated emergency. Radiat Res. 2013; 179(5):557-69. 10.1667/RR3196.1.
23. Romm H, Ainsbury E, Barnard S, Barrios L, Barquinero JF, Beinke C, et al. Automatic scoring of dicentric chromosomes as a tool in large scale radiation accidents. Mutat Res. 2013; 756(1-2):174-83. 10.1016/j.mrgentox.2013.05.013.
24. Oestreicher U, Endesfelder D, Gomolka M, Kesminiene A, Lang P, Lindholm C, et al. Automated scoring of dicentric chromosomes differentiates increased radiation sensitivity of young children after low dose CT exposure in vitro. Int J Radiat Biol. 2018; 94(11):1017-26. 10.1080/09553002.2018.1503429.
25. Lloyd DC, Edwards AA, Moquet JE, Guerrero-Carbajal YC. The role of cytogenetics in early triage of radiation casualties. Appl Radiat Isot. 2000; 52(5):1107-12. 10.1016/s0969-8043(00)00054-3.
26. Port M, Ostheim P, Majewski M, Voss T, Haupt J, Lamkowski A, et al. Rapid High-Throughput Diagnostic Triage after a Mass Radiation Exposure Event Using Early Gene Expression Changes. Radiat Res. 2019; 192(2):208-18. 10.1667/RR15360.1.
27. Ostheim P, Coker O, Schule S, Hermann C, Combs SE, Trott KR, et al. Identifying a Diagnostic Window for the Use of Gene Expression Profiling to Predict Acute Radiation Syndrome. Radiat Res. 2021; 195(1):38-46. 10.1667/RADE-20-00126.1.
28. Cruz-Garcia L, Nasser F, O'Brien G, Grepl J, Vinnikov V, Starenkiy V, et al. Transcriptional Dynamics of DNA Damage Responsive Genes in Circulating Leukocytes during Radiotherapy. Cancers (Basel). 2022; 14(11). 10.3390/cancers14112649.
29. Ostheim P, Don Mallawaratchy A, Muller T, Schule S, Hermann C, Popp T, et al. Acute radiation syndrome-related gene expression in irradiated peripheral blood cell populations. Int J Radiat Biol. 2021; 97(4):474-84. 10.1080/09553002.2021.1876953.
30. Grace MB, Moyer BR, Prasher J, Cliffer KD, Ramakrishnan N, Kaminski J, et al. Rapid radiation dose assessment for radiological

public health emergencies: roles of NIAID and BARDA. Health Phys. 2010; 98(2):172-8. 10.1097/01.HP.0000348001.60905.c0.

31. Ainsbury EA, Bakhanova E, Barquinero JF, Brai M, Chumak V, Correcher V, et al. Review of retrospective dosimetry techniques for external ionising radiation exposures. Radiat Prot Dosimetry. 2011; 147(4):573-92. 10.1093/rpd/ncq499.

32. Alexander GA, Swartz HM, Amundson SA, Blakely WF, Buddemeier B, Gallez B, et al. BiodosEPR-2006 Meeting: Acute dosimetry consensus committee recommendations on biodosimetry applications in events involving uses of radiation by terrorists and radiation accidents. Radiation Measurements. 2007; 42(6):972-96. https://doi.org/10.1016/j.radmeas.2007.05.035.

33. Trompier F, Bassinet C, Clairand I. Radiation accident dosimetry on plastics by EPR spectrometry. Health Phys. 2010; 98(2):388-94. 10.1097/01.HP.0000346334.78268.31.

34. Trompier F, De Angelis C, Monaca D, Sanità G, Roma S. Retrospective dose assessment in a radiation mass casualty by EPR and OSL in mobile phones2012.

35. McKeever SWS, Sholom S, Chandler JR. Developments in the Use of Thermoluminescence and Optically Stimulated Luminescence From Mobile Phones in Emergency Dosimetry. Radiat Prot Dosimetry. 2020; 192(2):205-35. 10.1093/rpd/ncaa208.

36. Beinke C, Siebenwirth C, Abend M, Port M. Contribution of Biological and EPR Dosimetry to the Medical Management Support of Acute Radiation Health Effects. Applied Magnetic Resonance. 2022; 53(1):265-87. 10.1007/s00723-021-01457-5.

37. Abend M, Amundson SA, Badie C, Brzoska K, Hargitai R, Kriehuber R, et al. Inter-laboratory comparison of gene expression biodosimetry for protracted radiation exposures as part of the RENEB and EURADOS WG10 2019 exercise. Sci Rep. 2021; 11(1):9756.

38. Abend M, Badie C, Quintens R, Kriehuber R, Manning G, Macaeva E, et al. Examining Radiation-Induced In Vivo and In Vitro Gene Expression Changes of the Peripheral Blood in Different Laboratories for Biodosimetry Purposes: First RENEB Gene Expression Study. Radiat Res. 2016; 185(2):109-23. 10.1667/RR14221.1.

39. Waldner L, Bernhardsson C, Woda C, Trompier F, Van Hoey O, Kulka U, et al. The 2019-2020 EURADOS WG10 and RENEB Field Test of Retrospective Dosimetry Methods in a Small-Scale Incident Involving Ionizing Radiation. Radiat Res. 2021; 195(3):253-64. 10.1667/RADE-20-00243.1.

40. Endesfelder D, Oestreicher U, Kulka U, Ainsbury EA, Moquet J, Barnard S, et al. RENEB/EURADOS field exercise 2019: robust dose estimation under outdoor conditions based on the dicentric chromosome assay. Int J Radiat Biol. 2021; 97(9):1181-98. 10.1080/09553002.2021.1941380.

41. Gregoire E, Barquinero JF, Gruel G, Benadjaoud M, Martinez JS, Beinke C, et al. RENEB Inter-Laboratory comparison 2017: limits and pitfalls of ILCs. Int J Radiat Biol. 2021; 97(7):888-905. 10.1080/09553002.2021.1928782.

42. Barquinero JF, Beinke C, Borras M, Buraczewska I, Darroudi F, Gregoire E, et al. RENEB biodosimetry intercomparison analyzing translocations by FISH. Int J Radiat Biol. 2017; 93(1):30-5. 10.1080/09553002.2016.1222092.

43. Moquet J, Barnard S, Staynova A, Lindholm C, Monteiro Gil O, Martins V, et al. The second gamma-H2AX assay intercomparison exercise carried out in the framework of the European biodosimetry network (RENEB). Int J Radiat Biol. 2017; 93(1):58-64. 10.1080/09553002.2016.1207822.

44. Terzoudi GI, Pantelias G, Darroudi F, Barszczewska K, Buraczewska I, Depuydt J, et al. Dose assessment intercomparisons within the RENEB network using G0-lymphocyte prematurely condensed chromosomes (PCC assay). Int J Radiat Biol. 2017; 93(1):48-57. 10.1080/09553002.2016.1234725.

45. Manning G, Macaeva E, Majewski M, Kriehuber R, Brzoska K, Abend M, et al. Comparable dose estimates of blinded whole blood samples are obtained independently of culture conditions and analytical approaches. Second RENEB gene expression study. Int J Radiat Biol. 2017; 93(1):87-98. 10.1080/09553002.2016.1227105.

46. Barnard S, Ainsbury EA, Al-hafidh J, Hadjidekova V, Hristova R, Lindholm C, et al. The first gamma-H2AX biodosimetry intercomparison exercise of the developing European biodosimetry network RENEB. Radiat Prot Dosimetry. 2015; 164(3):265-70. 10.1093/rpd/ncu259.

47. Barquinero J-F, Abe Y, N A, Endesfelder D, Georgieva D, Goh VST, et al. RENEB Inter-Laboratory Comparison 2021: The FISH-based translocation assay. Radiat Res 2023; 199.

48. Endesfelder D, Oestreicher U, Bucher M, Beinke C, Siebenwirth C, Ainsbury E, et al. RENEB Inter-Laboratory Comparison 2021: The Dicentric Chromosome Assay. Radiat Res 2023; 199.

49. Vral A, Endesfelder D, Balázs K, Beinke C, Cuceu Petrenci C, Finot F, et al. RENEB Inter-Laboratory Comparison 2021: The Cytokinesis-Block Micronucleus Assay. Radiat Res. 2023; 199:571–582.

50. Moquet J, Ainsbury E, Balázs K, Barnard S, Hristova R, Lumniczky K, et al. RENEB Inter-Laboratory Comparison 2021: The gamma-H2AX foci assay. Radiat Res 2023; 199.

51. Abend M, Amundson SA, Badie C, Brzoska K, Kriehuber R, Lacombe J, et al. RENEB Inter-Laboratory Comparison 2021: The gene expression assay Radiat Res 2023; 199.

52. Jaworska A, Ainsbury EA, Fattibene P, Lindholm C, Oestreicher U, Rothkamm K, et al. Operational guidance for radiation emergency response organisations in Europe for using biodosimetric tools developed in EU MULTIBIODOSE project. Radiat Prot Dosimetry. 2014; 164(1-2):165-9. 10.1093/rpd/ncu294.

53. Endesfelder D, Oestreicher U, JF B, Vral A, Terzoudi G, Moquet J, et al. What we have learned from RENEB inter-laboratory comparisons since 2012 with focus on ILC 2021. Radiat Res 2023; 199.

54. DIN 6809-5 Klinische Dosimetrie Teil 5: Anwendung von Röntgenstrahlen mit Röhrenspannungen von 100 bis 400 kV in der Strahlentherapie. 1996.

55. ISO 13304-2:2020 - Radiological Protection - Minimum Criteria For Electron Paramagnetic Resonance (EPR) Spectroscopy For Retrospective Dosimetry Of Ionizing Radiation - Part 2: Ex Vivo Human Tooth Enamel Dosimetry. International Organization for Standardization; 2020 2020-07.

56. Ivannikov AI, Tikunov DD, Borysheva NB, Trompier F, Skvortsov VG, Stepanenko VF, et al. Calibration of EPR signal dose response of tooth enamel to photons: experiment and Monte Carlo simulation. Radiat Prot Dosimetry. 2004; 108(4):303-15. 10.1093/rpd/nch040.

57. Fattibene P, Callens F. EPR dosimetry with tooth enamel: A review. Appl Radiat Isot. 2010; 68(11):2033-116. 10.1016/j.apradiso.2010.05.016.

58. Trompier F, Tikunov DD, Ivannikov A, Clairand I. ESR investigation of joint use of dentin and tooth enamel to estimate photon and neutron dose components of a mixed field. Radiat Prot Dosimetry. 2006; 120(1-4):191-6. 10.1093/rpd/nci650.

59. Ekendahl D, Judas L. Retrospective dosimetry with alumina substrate from electronic components. Radiat Prot Dosimetry. 2012; 150(2):134-41. 10.1093/rpd/ncr380.

60. Discher M, Greiter M, Woda C. Photon energy dependence and angular response of glass display used in mobile phones for accident dosimetry. Radiat Meas. 2014; 71:471-4. https://doi.org/10.1016/j.radmeas.2014.04.011.

61. Bassinet C, Pirault N, Baumann M, Clairand I. Radiation accident dosimetry: TL properties of mobile phone screen glass. Radiat Meas. 2014; 71:461-5. https://doi.org/10.1016/j.radmeas.2014.03.025.

62. Bassinet C, Woda C, Bortolin E, Della Monaca S, Fattibene P, Quattrini MC, et al. Retrospective radiation dosimetry using OSL of electronic components: Results of an inter-laboratory compar-

ison. Radiat Meas. 2014; 71:475-9. https://doi.org/10.1016/j.radmeas.2014.03.016.

63. Eakins JS, Hager LG, Kouroukla E, Smith RW, Tanner RJ. The Phe Fortuitous Dosimetry Capability Based on Optically Stimulated Luminescence of Mobile Phones. Radiat Prot Dosimetry. 2016; 170(1-4):412-5. 10.1093/rpd/ncv520.

64. BSI. ISO19238. 2014 International Organization for Standardization (ISO), radiation protection performance criteria for service laboratories performing biological dosimetry by cytogenetics. BSI 2014-02.

65. Hernández A, Endesfelder D, Einbeck J, Puig P, Benadjaoud A, Higueras M, et al. Biodose Tools: An R Shiny Application for Biological Dosimetry 2019 [Available from: https://aldomann.shinyapps.io/biodose-tools-beta/_w_7bf9e171/_w_b69c9547/_w_bd0125fb/.

66. DiCarlo AL, Homer MJ, Coleman CN. United States medical preparedness for nuclear and radiological emergencies. J Radiol Prot. 2021; 41(4). 10.1088/1361-6498/ac0d3f.

67. Discher M, Woda C, Ekendahl D, Rojas-Palma C, Steinhäusler F. Evaluation of physical retrospective dosimetry methods in a realistic accident scenario: Results of a field test. Radiation Measurements. 2021; 142:106544. https://doi.org/10.1016/j.radmeas.2021.106544.

68. Rojas-Palma C, Woda C, Discher M, Steinhäusler F. On the use of retrospective dosimetry to assist in the radiological triage of mass casualties exposed to ionising radiation. J Radiol Prot. 2020; 40(4). 10.1088/1361-6498/abc181.

69. Trompier F, Burbidge C, Bassinet C, Baumann M, Bortolin E, De Angelis C, et al. Overview of physical dosimetry methods for triage application integrated in the new European network RENEB. Int J Radiat Biol. 2017; 93(1):65-74. 10.1080/09553002.2016.1221545.

70. Farese AM, MacVittie TJ. Filgrastim for the treatment of hematopoietic acute radiation syndrome. Drugs Today (Barc). 2015; 51(9):537-48. 10.1358/dot.2015.51.9.2386730.

71. Herodin F, Drouet M. Cytokine-based treatment of accidentally irradiated victims and new approaches. Exp Hematol. 2005; 33(10):1071-80. 10.1016/j.exphem.2005.04.007.

72. Rothkamm K, Horn S, Scherthan H, Rossler U, De Amicis A, Barnard S, et al. Laboratory intercomparison on the gamma-H2AX foci assay. Radiat Res. 2013; 180(2):149-55. 10.1667/RR3238.1.

73. Badie C, Kabacik S, Balagurunathan Y, Bernard N, Brengues M, Faggioni G, et al. Laboratory intercomparison of gene expression assays. Radiat Res. 2013; 180(2):138-48. 10.1667/RR3236.1.

74. Jacobs AR, Guyon T, Headley V, Nair M, Ricketts W, Gray G, et al. Role of a high throughput biodosimetry test in treatment prioritization after a nuclear incident. Int J Radiat Biol. 2020; 96(1):57-66. 10.1080/09553002.2018.1532615.

75. Gu J, Norquist A, Brooks C, Repin M, Mukherjee S, Lacombe J, et al. Development of an integrated fingerstick blood self-collection device for radiation countermeasures. PLoS One. 2019; 14(10):e0222951. 10.1371/journal.pone.0222951.

76. Beinke C, Barnard S, Boulay-Greene H, De Amicis A, De Sanctis S, Herodin F, et al. Laboratory intercomparison of the dicentric chromosome analysis assay. Radiat Res. 2013; 180(2):129-37. 10.1667/RR3235.1.

77. Discher M, Hiller M, Woda C. MCNP simulations of a glass display used in a mobile phone as an accident dosimeter. Radiation Measurements. 2015; 75:21-8. https://doi.org/10.1016/j.radmeas.2015.02.013.

78. Kim H, Yu H, Discher M, Kim MC, Choi Y, Lee H, et al. A small-scale realistic inter-laboratory accident dosimetry comparison using the TL/OSL from mobile phone components. Radiation Measurements. 2022; 150:106696. https://doi.org/10.1016/j.radmeas.2021.106696.

79. Chandler JR, Sholom S, McKeever SWS, Bakhanova E, Chumak V, Velásquez D, et al. Dose conversion factors for absorbed dose in a mobile phone to absorbed dose in critical organs in an anthropomorphic phantom for emergency dosimetry applications: OSL and TL experimental results, and Monte Carlo simulations. Radiat Meas. 2022; 154:106781. https://doi.org/10.1016/j.radmeas.2022.106781.

80. Eakins JS, Kouroukla E. Luminescence-based retrospective dosimetry using Al2O3 from mobile phones: a simulation approach to determine the effects of position. J Radiol Prot. 2015; 35(2):343-81. 10.1088/0952-4746/35/2/343.

81. Kim MC, Kim H, Han H, Lee J, Lee SK, Chang I, et al. A study on dose conversion from a material to human body using mesh phantom for retrospective dosimetry. Radiat Meas. 2019; 126:106126. https://doi.org/10.1016/j.radmeas.2019.106126.

82. Discher M, Eakins J, Woda C, Tanner R. Translation of the absorbed dose in the mobile phone to organ doses of an ICRP voxel phantom using MCNPX simulation of an Ir-192 point source. Radiat Meas. 2021; 146:106603. https://doi.org/10.1016/j.radmeas.2021.106603.

83. Marciniak A, Juniewicz M, Ciesielski B, Prawdzik-Dampc A, Karczewski J. Comparison of three methods of EPR retrospective dosimetry in watch glass. Frontiers in Public Health. 2022; 10. 10.3389/fpubh.2022.1063769.

84. Scherthan H, Hieber L, Braselmann H, Meineke V, Zitzelsberger H. Accumulation of DSBs in gamma-H2AX domains fuel chromosomal aberrations. Biochem Biophys Res Commun. 2008; 371(4):694-7. 10.1016/j.bbrc.2008.04.127.

85. Rothkamm K, Barnard S, Moquet J, Ellender M, Rana Z, Burdak-Rothkamm S. DNA damage foci: Meaning and significance. Environ Mol Mutagen. 2015; 56(6):491-504. 10.1002/em.21944.

86. Riecke A, Rufa CG, Cordes M, Hartmann J, Meineke V, Abend M. Gene expression comparisons performed for biodosimetry purposes on in vitro peripheral blood cellular subsets and irradiated individuals. Radiat Res. 2012; 178(3):234-43. 10.1667/rr2738.1.

87. Agbenyegah S, Abend M, Atkinson MJ, Combs SE, Trott KR, Port M, et al. Impact of Inter-Individual Variance in the Expression of a Radiation-Responsive Gene Panel Used for Triage. Radiat Res. 2018; 190(3):226-35. 10.1667/RR15013.1.

88. Rothkamm K, Balroop S, Shekhdar J, Fernie P, Goh V. Leukocyte DNA damage after multi-detector row CT: a quantitative biomarker of low-level radiation exposure. Radiology. 2007; 242(1):244-51. 10.1148/radiol.2421060171.

89. Redon CE, Nakamura AJ, Gouliaeva K, Rahman A, Blakely WF, Bonner WM. Q(gamma-H2AX), an analysis method for partial-body radiation exposure using gamma-H2AX in nonhuman primate lymphocytes. Radiat Meas. 2011; 46(9):877-81. 10.1016/j.radmeas.2011.02.017.

90. Ainsbury EA, Livingston GK, Abbott MG, Moquet JE, Hone PA, Jenkins MS, et al. Interlaboratory variation in scoring dicentric chromosomes in a case of partial-body x-ray exposure: implications for biodosimetry networking and cytogenetic ''triage mode'' scoring. Radiat Res. 2009; 172(6):746-52. 10.1667/RR1934.1.

91. Vinnikov VA, Ainsbury EA, Maznyk NA, Lloyd DC, Rothkamm K. Limitations associated with analysis of cytogenetic data for biological dosimetry. Radiat Res. 2010; 174(4):403-14. 10.1667/RR2228.1.