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POSSIBILITIES AND LIMITATIONS OF FLUORESCENCE *IN SITU* HYBRIDIZATION TECHNIQUE IN RETROSPECTIVE DETECTION OF LOW DOSE RADIATION EXPOSURE IN POST-CHERNOBYL HUMAN COHORTS

Cytogenetic analysis using the fluorescence in situ hybridisation (FISH) technique was performed late time after the Chernobyl accident in groups of liquidators, evacuees from 30 km exclusive zone, residents of radioactively contaminated areas and control donors age-matched to exposed persons. Stable and unstable chromosome type exchanges were recorded using a hybrid conventional-PAINT nomenclature. The mean yield of stable chromosome exchanges in liquidators did not correlate with registered radiation doses but had a clear negative dependence on the duration of liquidators' staying in Chernobyl zone, that was in a good agreement with early data based on conventional dicentrics plus rings analysis. The overspontaneous excess for stable chromosome exchange level appeared to be higher in evacuees 16—40 years old than that of senior persons, whereas no age-dependent difference occurred for initially induced dicentrics plus rings yields in this cohort. The stable chromosome exchange yield, as well as combined yield of dicentrics plus rings and potentially unstable incomplete translocations in residents of radioactively contaminated areas showed a reasonable positive correlation with levels of ^{137}Cs contamination. The observed yields of stable chromosome exchanges in all three exposed groups appeared to be somewhat lower than those of expected from unstable exchange-based doses which were referred to an in vitro dose response of stable exchanges outcome in human lymphocytes. Thus, FISH analysis can be successfully applied for qualitative cytogenetic indication of past and chronic radiation exposure to low doses but further refinement of FISH-based system for quantitative dose assessment is still required. Some practical approaches of solving this task are discussed.

Introduction. The main application of cytogenetics research in human radiobiology comprises direct evaluation of chromosomal damage caused by ionising radiation in human cells and reversal task of accumulated radiation dose reconstruction using the chromosome aberration yield as the end-point. The Chernobyl accident caused the necessity of large-scale cytogenetic surveys of human cohorts exposed to low-dose radiation, i.e in participants of clean-up operations, evacuees from the exclusive zone and persons who continued to live in areas contaminated with radionuclides. Chromosomal biodosimetry in post-Chernobyl critical groups became especially challenging in late terms after the accident, when the conventional cytogenetic technique turned to be unreliable due to elimination of lymphocytes carrying unstable aberrations, meanwhile the methods based on stable chromosome rearrangements quantification still required methodological development.

Fluorescence *in situ* hybridization (FISH) technique brought a significant advantage of rapid scoring of stable aberrations, but also some limitations in FISH biodosimetry were recognised. The problems were related to difficulties of proper dose-response calibration of the system and its limited sensitivity within low dose range, positive age-effect relationship for spontaneous level and rather questionable stability of translocation yield after irradiation *in vivo*. In general, it became obvious that both measuring of stable aberration level and biodosimetrical interpreting of FISH data have to be based on logical approaches somewhat different from that of routine dicentric analysis.

The aims of our work were to compare the results of early and late cytogenetic investigations in Chernobyl groups and to demonstrate the approaches which may strengthen the possibilities of FISH assay in detection of past or chronic low dose radiation exposure.

Materials and methods. Groups of persons surveyed by FISH technique consisted of 16 liquidators who took part in clean-up operations at Chernobyl zone in 1986—1987, 18 former citizens of t. Pripiat' and nearby villages who were evacuated soon after the accident, 21 Belorussian residents of radioactively contaminated areas and 12 unexposed control donors. Blood samples for cytogenetic analysis were collected 12.8—14.8 years after the Chernobyl accident in

evacuees and inhabitants and 9.5—14.8 years after the end of duty at Chernobyl in liquidators. Age of investigated persons varied within 35—48 years (mean 41 years) in liquidators, 16—55 years (mean 40 years) in evacuees, 15—26 years (mean 21 years) in inhabitants and 19—58 years (mean 39 years) in controls. All the liquidators, evacuees and control donors were surveyed at the Institute of Medical Radiology (Kharkiv, Ukraine). Samples from Belarus and corresponding information concerning radionuclide contamination levels at living places were provided by our colleagues from the Institute of Genetics and Cytology (Minsk, Belarus).

For cytogenetic assay the standard PHA-stimulated lymphocyte cultures were set up for 48 hrs, metaphases were harvested after 4 h colchicin treatment and fixed in methanol/acetic acid mixture [1]. Coded slides from each sample were processed by FISH technique [2]. Slides were FITC painted, highlighting chromosome combinations 1, 2 and 4 or 6, 9, 15 and 21 (Cambio), the other chromosomes were counterstained with DAPI and all centromeres were marked with probes, which fluoresced red (Oncor). Aberrations involving FITC-highlighted chromosomes were recorded using our modification of the hybrid conventional/PAINT descriptive nomenclature; scoring criteria were published earlier [3, 4]. The spectrum of chromosome rearrangements included in present analysis consisted of painted dicentrics and centric rings accompanied by fragments, insertions and translocations. The latter were recognised as complete t_{comp} or incomplete tAb (painted fragment attached to the non-painted chromo-

Aberration levels measured by FISH technique in liquidators, evacuees and inhabitants of radioactively contaminated areas late time after the Chernobyl accident

Group	*n*	GE	Aberration yields ±SE per 100 genome equivalents					
			Dic + CR	t_{comp}	t_{inc}*	t_{inc+ac}	t_{inc}MP	Ins
Liquidators								
Doses in documents, mGy								
48—200	5	338	0.00	0.30 ± 0.30	0.89 ± 0.51	0.00	0.89 ± 0.51	0.00
250	6	980	0.31 ± 0.18	0.82 ± 0.29	0.00	0.00	1.22 ± 0.35	0.20 ± 0.14
300—978	5	905	0.22 ± 0.16	0.77 ± 0.29	0.22 ± 0.16	0.00	1.10 ± 0.35	0.11 ± 0.11
Staying in Chernobyl zone, days								
9—44	9	861	0.23 ± 0.16	0.93 ± 0.33	0.35 ± 0.20	0.00	0.93 ± 0.33	0.23 ± 0.16
60—122	7	1362	0.22 ± 0.13	0.59 ± 0.21	0.15 ± 0.10	0.00	1.25 ± 0.30	0.07 ± 0.07
Total liquidators	16	2223	0.22 ± 0.10	0.72 ± 0.18	0.22 ± 0.10	0.00	1.12 ± 0.22	0.13 ± 0.08
Evacuees								
Age, years								
16—40	8	2419	0.21 ± 0.09	0.45 ± 0.14	0.29 ± 0.11	0.00	0.87 ± 0.19	0.17 ± 0.08
44—55	10	2863	0.14 ± 0.07	0.66 ± 0.15	0.24 ± 0.09	0.07 ± 0.05	0.94 ± 0.18	0.11 ± 0.06
Total evacuees	18	5282	0.17 ± 0.06	0.57 ± 0.10	0.27 ± 0.07	0.04 ± 0.03	0.91 ± 0.13	0.13 ± 0.05
Residents of radioactively contaminated areas								
Level of ^{137}Cs deposition, kBq/m^2								
R1: 1.5—44	8	3159	0.13 ± 0.06	0.22 ± 0.08	0.06 ± 0.04	0.06 ± 0.04	0.47 ± 0.12	0.06 ± 0.04
R2: 110—860	13	4757	0.08 ± 0.04	0.34 ± 0.08	0.06 ± 0.04	0.25 ± 0.07	0.55 ± 0.11	0.11 ± 0.05
Total residents	21	7916	0.10 ± 0.04	0.29 ± 0.07	0.06 ± 0.03	0.18 ± 0.05	0.52 ± 0.08	0.09 ± 0.03
Controls								
Age, years								
19—26[a]	4	1102	0.09 ± 0.09	0.27 ± 0.16	0.00	0.00	0.45 ± 0.20	0.00
19—36[b]	7	2180	0.09 ± 0.06	0.28 ± 0.11	0.09 ± 0.06	0.00	0.50 ± 0.15	0.05 ± 0.05
43—58[b]	5	1908	0.10 ± 0.07	0.47 ± 0.09	0.10 ± 0.07	0.10 ± 0.07	0.79 ± 0.20	0.10 ± 0.07
Total controls	12	4088	0.10 ± 0.05	0.37 ± 0.09	0.10 ± 0.05	0.05 ± 0.03	0.64 ± 0.12	0.07 ± 0.04

GE — genome equivalents; *n* — number of persons; SE — standard errors for the mean; Dic + CR — dicentrics and centric rings; t_{comp} — complete translocations; t_{inc}*, t_{inc+ac}, t_{inc}MP — incomplete translocations; Ins — insertions; controls [a] — for comparing with residents; controls [b] — for comparing with corresponding age groups of evacuees.

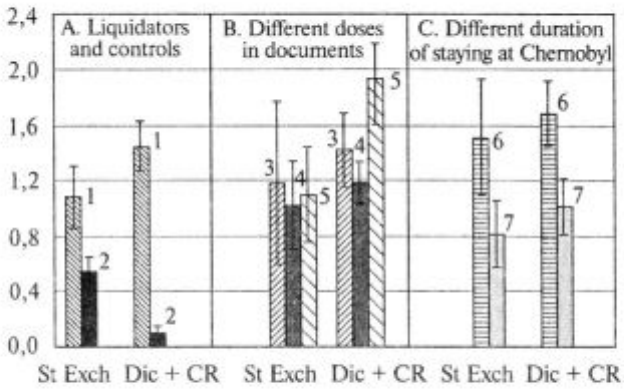

Fig. 1. Comparison of stable chromosome exchange yields (St Exch) measured 9.5—14.8 years after exposure with dicentrics plus centric rings levels (Dic + CR) observed during 1 year post-irradiation in Chernobyl liquidators: 1 — total liquidators; 2 — reference control; 3, 4 and 5 — liquidators with documented doses <250, 250 and >250 mGy, respectively; 6 and 7 — liquidators with duration of staying in the Chernobyl zone <2 months and >2 months, respectively; ordinate axis — aberration yield per 100 cells

some), tBa* (involving a visibly unshortened painted chromosome), tBa + ac (accompanied by a fragment from the painted chromosome) and tBaMP (involving a markedly shortened painted chromosome with no missing fragment present somewhere in the cell — «missing part»).

Numbers of actually scored cells were converted into genome equivalents using Lucas' formula [5]. Individual scoring data were pooled within groups; weighted mean aberration yields were expressed per 100 genome equivalents. Standard errors for the means were calculated from the dispersion of aberration per cell distributions. In final data analysis the yields of incomplete translocations of different types (t_{inc}*, t_{inc+ac} and t_{inc}MP) were estimated within the sum of tAb and tBa, as described previously [4]. Intergroup data comparison was performed with Student's *t*-test applying numbers of genome equivalents as weighting factor.

Results and discussion. Mean yields of chromosome aberrations detected by FISH analyses in surveyed groups are shown in Table. Liquidators were divided into subgroups according to documented irradiation doses and duration of staying at the Chernobyl zone. Residents of radioactively contaminated areas were divided in subgroups R1 and R2 according to ^{137}Cs contamination levels at their living places. Evacuees and control donors were divided in subgroups depending on age.

In the control group a clear tendency of aberration yields increasing with persons' age was observed for all types of chromosome exchanges specifically detected by FISH technique. Therefore, cytogenetic indices in liquidators and total evacuees groups were compared directly to those of in total controls due to similarity of mean age. Additionally, age subgroups of evacuees were matched to correspondent age subgroups of control donors. Spontaneous aberration levels for residents of contaminated areas were derived from the separate subgroup of young controls only.

In our recent work we constructed a practically applicable FISH-biodosimetry system based on setting up a calibration curve *in vitro* for those types of chromosome rearrangements, which were undoubtedly specific to radiation, showed a strong positive dose dependence in human G_0 lymphocytes and might have a potential stability with time after irradiation [4]. According to such requirements, the end-point of choice for FISH detection of past exposure was a combined yield of insertions, t_{comp} and t_{inc}*; the latter probably represented reciprocal exchanges involving a small telomeric region beyond the limits of visual resolution by FISH. The levels of stable chromosome exchanges with full presence of chromosomal material in «stable» cells (St Exch) in liquidators and evacuees comparing with control values are presented on Figs 1 and 2. The yields of dicentrics plus centric rings (Dic + CR) measured during the first year after irradiation in accordingly formed groups of exposed persons are also shown.

The level of St Exch statistically exceeded the spontaneous yield in total liquidators and total evacuees groups ($t = 2.45$ and 2.30, respectively; $p < 0.05$). This parameter didn't correlate with irradiation dose recorded in liquidators' documents but appeared to be nearly twice higher in persons who spent less than 2 months in Chernobyl zone comparing with liquidators who's duration of duty exceeded 2 months. Such results strongly corresponded to our early data, when the similar decrease of Dic + CR yield in liquidators with recorded doses 250 mGy comparing with other dose subgroups was observed, and a significant negative relationship between

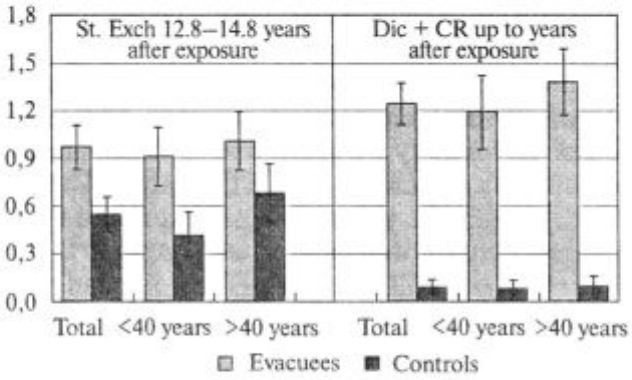

Fig. 2. Late stable chromosome exchanges yields (St Exch) and early dicentrics plus centric rings levels (Dic + CR) in evacuees from 30 km Chernobyl exclusive zone depending on their age, in compare with reference control: ordinate axis — aberration yield per 100 cells

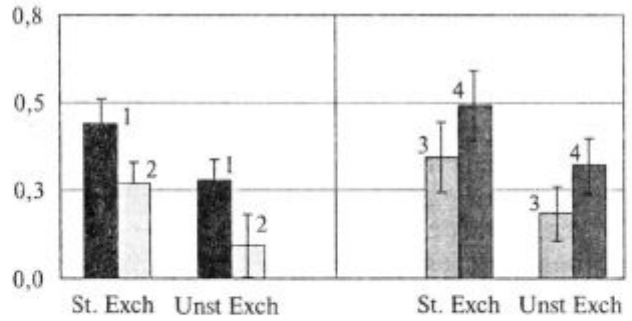

Fig. 3. FISH-based estimations of stable chromosome exchange (St Exch) and unstable chromosome exchange (Unst Exch) yields in residents of radioactively contaminated areas, who were sampled 12.8—14.8 years after the Chernobyl accident: 1 — total residents; 2 — reference control; 3 and 4 — subgroups of residents living on territories with levels of ^{137}Cs contamination 1.5—44 and 110—860 kBq/m^2, respectively; ordinate axis — aberration yield per 100 cells

unstable aberration level and exposure duration was also detected.

The age dependence of St Exch level in evacuees was much less pronounced than that of in control donors, thus the overspontaneous excess of the parameter was statistically significant in younger subgroups of evacuees ($t = 2.08$; $p < 0.05$), but not in persons 44—55 years old ($p > 0.05$). That contrasted with early observation when the magnitude of difference between evacuees and controls for Dic + CR yield during 1 year after exposure nearly coincided in younger and senior subgroups.

In total group of residents of radioactively contaminated areas the mean yield of St Exch was 1.6 times higher than in age-matched controls, and the overspontaneous values in R1 and R2 subgroups had a 3-fold difference (Fig. 3). A comparison of «stable» and «unstable» cytogenetic damage levels in residents became a really challenging task. The mean yield of Dic + CR alone did not show a positive correlation with levels of ^{137}Cs contamination. But in addition to Dic + CR, a significant number of t_{inc+ac} was detected in residents of radioactively contaminated areas, that obviously reflected the radiation induction of these exchanges directly in mature lymphocytes, as it took place in conditions of in vitro exposure [4]. So, t_{inc+ac} were considered as analogues of dicentrics and centric rings, and the combined yield of Dic + CR and t_{inc+ac} (Unst Exch) in total residents group appeared to be 3 times higher than that of in young controls. Moreover, the difference for this parameter between R1 and R2 subgroups occurred in manner analogous to that observed for St Exch.

Thus, the results of stable and unstable chromosome exchange analyses provided a reasonable mutual correspondence of cytogenetic characteristics in different groups of exposed persons. However, for strengthening a conclusion about the radiobiological conformity of these *in vivo* data, the difference between dose responses for stable and unstable chromosome exchanges outcome in human lymphocytes needs to be taken into account. Recently we demonstrated that average Dic + CR yields in randomised groups of liquidators and evacuees sampled soon after exposure could be converted into respective doses about 460 and 360 mGy of protracted irradiation through a linear coefficient of the dose response curve $2.98 \cdot 10^{-2} \cdot Gy^{-1}$ per cell [6, 7]. Applying these doses to the linear term $1.40 \cdot 10^{-2} \cdot Gy^{-1}$ per cell of St Exch outcome *in vitro* [4], the overspontaneous St Exch yields were expected to be about 0.64 per 100 cells in total liquidators and 0.50 per 100 cells in total evacuees, but 15 % lower values were really observed in each group.

Unlike liquidators and evacuees, who were irradiated protractedly, residents of radioactively contaminated areas underwent long term

chronic exposure. Studied subgroups R1 and R2 had respective average duration of exposure 13.8 and 14.6 years. In such case utilising unstable chromosome exchanges for biological dosimetry implies simultaneous considering an elimination of «old» aberrant cells and aberration formation *de novo* in circulating lymphocytes that can be done using the formula suggested by Sasaki [8]. Applying to this formula an aberrant lymphocyte mean half-life 2.24 years (which was empirically established in persons exposed to low dose radiation [9]) and the linear term $4.79 \cdot 10^{-2} \cdot Gy^{-1}$ per cell for dose response of combined yield of Dic + CR and t_{inc+ac} (that was estimated from previously published data of *in vitro* experiment [4]) corresponding chronic doses about 90 and 220 mGy were calculated for R1 and R2 subgroups. At these doses the radiation-induced yields of St Exch were expected to be about 0.13 and 0.31 per 100 cells, that were higher than really observed 0.08 and 0.23 per 100 cells in R1 and R2 subgroups, respectively.

So, even with a significantly lower production of St Exch per unit dose comparing with Dic + CR or Unst Exch the observed levels of stable chromosome exchanges in all three groups of exposed persons appeared to be systematically lower than those of expected from unstable exchange-based dose assessments. This finding is well in line with the results of other surveys in which late translocations versus early dicentrics plus rings levels comparison was carried out in persons irradiated to high doses [10, 11]. In our opinion, such inconsistency can be explained by the following reasons.

1. Different contents of groups sampled early and late time after exposure. That explanation is applicable in liquidators and evacuees, but not in residents of contaminated areas, because in latter case both data sets were obtained within the same individuals.

2. Partial elimination of cells with stable exchanges during proliferation of lymphatic stem cells, in which these rearrangements were initially induced. An inherent lethality of balanced chromosome exchanges for actively dividing cells were recognised in studies of aberration transmission through sequential mitoses *in vitro* after irradiation even to low doses [12, 13], and some declining of radiation-induced translocation yield with time was also shown *in vivo* by individual follow-up FISH surveys in radiation accident victims [10, 14].

3. Non-identical translocations outcome per unit dose in lymphocyte precursors and mature lymphocytes whereas latter are usually used for setting up calibration curves. The issue is related to varying of chromosomal radiosensitivity through mitotic cycle and changing of aberration types, which are mainly induced by irradiation at G_1, S and G_2 stages in proliferating cells.

Taking into account two latter reasons the constructing *in vitro* calibration curves for translocations in G_0 lymphocytes even with aberration scoring concentrated on «stable» cells only, that had been suggested as the most advanced approach of improving FISH-biodosimetry, seems to be not sufficient enough. In trying to overcome the problem of refining the FISH-biodosimetry system, different approaches can be suggested. One is related to direct engaging of *in vivo* data and includes either evaluating translocation elimination intensity by individual follow-up FISH analyses [14], or deriving a dose response for truly stable aberrations from the results obtained late time after exposure in irradiated persons with precisely known accumulated doses [15]. Another way comprises constructing a radiobiological model *in vitro*, which may reasonably approximate the real conditions of *in vivo* exposure and subsequent survival of aberrations in lymphocyte precursors. Our current activity involves extensive research in both directions in hope to develop an optimized FISH-based system for retrospective biological dosimetry.

Conclusions. The results of our investigations clearly indicate that a FISH assay may serve as powerful tool for measuring the cytogenetic damage resulted from past irradiation when conventional analysis became insufficient due to elimination of lymphocytes with unstable aberrations as it took place in liquidators and evacuees. The combined quantification of FISH-detectable dicentrics plus rings and expectedly unstable proportion of incomplete translocations allowed to enhance the sensitivity of biological indication of low dose rate chronic exposure in residents of radioactively contaminated

areas. Generally, stable and unstable chromosome exchange analyses provided a reasonable mutual correspondence of cytogenetic characteristics in different groups of exposed persons. The problem remained was the natural age-dependent increase of spontaneous translocation level that limited the accuracy of radiation-related stable exchange yield evaluation in persons of senior age, e.g. in some evacuees in our study.

The observed levels of stable chromosome exchanges in all three groups of exposed persons appeared to be somewhat lower than those of expected from unstable exchange-based doses, referred to an *in vitro* dose response outcome of stable exchanges in human lymphocytes. Thus, a further development of practically applicable FISH-biodosimetry system is required, and for solving this task a significant body of data still need to be accumulated from both *in vitro* experiments and *in vivo* studies.

РЕЗЮМЕ. Проведено исследование цитогенетических показателей методом флюоресцентной *in situ* гибридизации (FISH) в отдаленные сроки после Чернобыльской аварии в группах ликвидаторов, эвакуированных жителей 30 км зоны ЧАЭС, жителей радиоактивно загрязненных территорий и адекватных по возрасту контрольных доноров. Стабильные и нестабильные обмены хромосомного типа регистрировали с использованием гибридной классической PAINT-номенклатуры. Уровень стабильных хромосомных обменов у ликвидаторов не проявил корреляции с дозами облучения по документам, однако имел четкую обратную зависимость от длительности пребывания в зоне ЧАЭС, что хорошо соответствовало полученной путем классического анализа ранней цитогенетической картине по частоте дицентриков и колец. Надспонтанный эксцесс частоты стабильных хромосомных обменов у эвакуированных оказался выше в возрастной группе 16—40 лет по сравнению с лицами старшего возраста на фоне отсутствия возрастной зависимости для начального уровня дицентриков и колец в данной когорте. У жителей радиоактивно загрязненных территорий уровень стабильных хромосомных обменов, равно как и суммарная частота дицентриков, колец и потенциально нестабильных неполных транслокаций, проявил значимую положительную корреляцию с уровнем контаминации ^{137}Cs в местах проживания. Реальный уровень стабильных хромосомных обменов во всех трех группах лиц чернобыльского контингента оказался несколько ниже значений, ожидаемых исходя из оценок доз по частоте нестабильных обменов. Таким образом, методика FISH может успешно применяться для качественной цитогенетической индикации отдаленного или хронического облучения в низких дозах, однако система количественной оценки доз облучения на основании FISH-исследования требует дальнейшего усовершенствования. Обсуждаются возможные практические подходы к решению этой задачи.

РЕЗЮМЕ. Проведено дослідження цитогенетичних показників методом флуоресцентної *in situ* гібридізації (FISH) у віддалені строки після Чорнобильської аварії в групах ліквідаторів, евакуйованих мешканців 30 км зони ЧАЕС, мешканців радіоактивно забруднених територій та адекватних за віком контрольних донорів. Стабільні та нестабільні обміни хромосомного типу реєстрували з використанням гібридної класичної PAINT-номенклатури. Рівень стабільних хромосомних обмінів у ліквідаторів не проявив кореляції з дозами опромінення за документами, проте мав чітку зворотню залежність від тривалості перебування в зоні ЧАЕС, що відповідало отриманій шляхом класичного аналізу ранній цитогенетичній картині за частотою дицентриків і кілець. Надспонтанний ексцес частоти стабільних хромосомних обмінів у евакуйованих виявився вищим у віковій групі 16—40 років порівняно з особами старшого віку на тлі відсутності вікової залежності для початкового рівня дицентриків і кілець в даній когорті. У мешканців радіоактивно забруднених територій рівень стабільних хромосомних обмінів, як і сумарна частота дицентриків, кілець та потенційно нестабільних неповних транслокацій, проявив значущу позитивну кореляцію з рівнем контамінації ^{137}Cs в місцях мешкання. Реальні рівні стабільних хромосомних обмінів в усіх трьох групах осіб чорнобильського контингенту виявилися дещо нижчими, ніж значення, що очікувалися, виходячи з оцінок доз за частотою нестабільних обмінів. Таким чином, методика FISH може успішно використовуватися для якісної цитогенетичної індикації віддаленого або хронічного опромінення в низьких дозах, але система кількісної оцінки доз опромінення на підставі FISH-дослідження потребує подальшого удосконалення. Обговорюються можливі практичні підходи до вирішення цієї задачі.

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