

## AGEING AND PRODUCTION OF THE CYTOKINES IN CHERNOBYL CLEAN-UP WORKERS FROM LATVIA

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*Chronic low-grade inflammation with subsequent impairment of immune system function promotes the development of age-related diseases, such as cancers, degenerative and infection diseases. It is not yet clear, if exposure to ionising radiation accelerates the aging process. The aim of the present work was to estimate the production of several cytokines by peripheral blood cells of Latvia's Chernobyl clean-up workers depending on age. ELISA was employed to determine the plasma level of sIL-1 $\beta$  and sIL-6 as well as level of IL-4 and TNF- $\alpha$  spontaneous and 24h and 96h after in vitro stimulation of peripheral blood mononuclear cell cultures by lipopolysaccharide (LPS) and phytohemagglutinin (PHA) mitogens were determined in 40 Chernobyl clean-up workers 17 years after their work in Chernobyl and in 42 blood-donors without a history of occupational radiation exposure. The ability of peripheral blood leukocytes (PBL) to produce interferons (IFNs) was determined in 73 Chernobyl clean-up workers 15 years after the work in Chernobyl and in age-matched 63 blood-donors. IFNs were tested in whole blood cultures by standard virus cytopathic inhibition micromethod after their in vitro induction by Newcastle disease virus, phytohemagglutinin or double-stranded RNA. Individuals were divided into three age groups: age < 40, age 40–49 and age > 50. The ability of PBL to produce IFN was significantly decreased in all Chernobyl clean-up worker age groups in comparison with blood-donors (control groups). The incidence of good ability to produce IFN gradually decreased with age in the control group, but increased with age in aged-matched Chernobyl clean-up workers groups. The production TNF- $\alpha$  and IL-4 by peripheral blood mononuclear cells as well as sIL-1 $\beta$  level in plasma showed no significant differences between all the examined age groups. The sIL-6 level was gradually increased with age in Chernobyl clean-up workers. Our results showed that the concentration of pro-inflammation cytokine sIL-6 in peripheral blood plasma, as well as the ability of PBL to produce IFNs, in Chernobyl clean-up workers from Latvia is age dependent.*

**Key words:** ageing, Chernobyl accident, IL-4, sIL-6, sIL-1 $\beta$ , TNF- $\alpha$ , IFNs, cell immunity.

### INTRODUCTION

It is still not clear if exposure to ionizing radiation accelerates the ageing process (Sasaki *et al.*, 1991; Chumak *et al.*, 2001). Information about changes in different parts of the immune system by ageing are contradictory (De Paoli *et al.*, 1988; Rea *et al.*, 1996; Bruunsgard *et al.*, 2000; Yen *et al.*, 2000; Nerlan *et al.*, 2002; Schindovski *et al.*, 2002). Recent investigations confirm ageing to be associated with increased inflammatory activity reflected by increased levels of circulating proinflammatory cytokines (Franceschi *et al.*, 2000; Franceschi and Bonafe, 2003). Chronic low-grade inflammation with subsequent impairment of immune system function during aging promotes the development of age-related diseases, such as cancers, degenerative and infection

diseases. In the same way, increased inflammatory activities have been observed after radiation exposure (Qurmy *et al.*, 1999; Van Der Meeren *et al.*, 1999).

Approximately 6,000 men in Latvia were affected by ionising radiation during work in Chernobyl to clean up the after-effects of the Chernobyl power plant accident. Morbidity of workers increased progressively year by year significantly exceeding that of the overall population (Brūvere *et al.*, 2002).

The aim of the present work was to determine the production of several cytokines by peripheral blood cells of Chernobyl clean-up workers depending on age.

## MATERIALS AND METHODS

A total of 113 Chernobyl clean-up workers (who participated during 1986 in the clean-up work), 15–17 years after the work in Chernobyl, and 105 blood-donors (Latvia's men) without a history of occupational radiation exposure were examined in this study.

The ability of peripheral blood leukocytes (PBL) to produce IFNs was determined in 73 Chernobyl clean-up workers and in 63 age-matched blood-donors. Other cytokines (sIL-1 $\beta$ , sIL-6, IL-4, TNF- $\alpha$ ) as well as lymphocytes subpopulations were determined in 40 Chernobyl clean-up workers 17 years after they worked in Chernobyl and in 42 blood donors. Individuals were divided in three age groups: age < 40, age 40–49 and age > 50.

Plasma concentrations of soluble IL-1 $\beta$  and IL-6 cytokines were measured by ELISA (R&D systems, Minneapolis, USA). Level IL-4 and TNF- $\alpha$  spontaneous and after stimulation by lipopolysaccharide (LPS) and phytohemagglutinin (PHA) mitogens after 24 h and 96 h in peripheral blood mononuclear cell (PBMC) culture supernatants were measured by ELISA (Biosource International, Belgium). IFNs were tested in whole blood cultures by the standard virus cytopathic inhibition micromethod after their *in vitro* induction by Newcastle disease virus, phytohemagglutinin or double-stranded RNA. The number of PBL, monocytes, lymphocytes and their subpopulations (CD3+, CD4+, CD8+, CD16+, CD19+, CD25+) were determined by flow cytometry using the appropriate specific monoclonal antibodies Becton Dickenson, USA in the peripheral blood.

The levels of immunoglobulins (IgA, IgG and IgM) were detected by nephelometry in the blood serum.

**Statistical analysis.** Data were statistically analysed using the ANOVA test. The level of significance was set at  $P < 0.05$ .

## RESULTS

**The incidence of good ability of PBL to produce IFNs (100–400 IU) was significantly decreased in Chernobyl clean-up workers in comparison with blood-donors (control group) (Fig. 1a,1b,1c). An exception was the 2 years age Chernobyl clean-up worker group) (Figure 1c). In this group the incidence of good ability to produce IFN after induction by PHA was significantly higher than that in the age-matched blood donors. The incidence of good ability of PBL to produce IFNs induced by PHA significantly increased with age in Chernobyl clean-up workers, while the incidence of good ability to produce IFN gradually decreased with age (by each of the three inducers) in the control group.**

**The incidence of inability to produce IFN in the youngest Chernobyl clean-up worker group (< 40) was significantly greater in comparison with the age-matched control group (Fig. 2a). At age 40–49 years, the difference between**

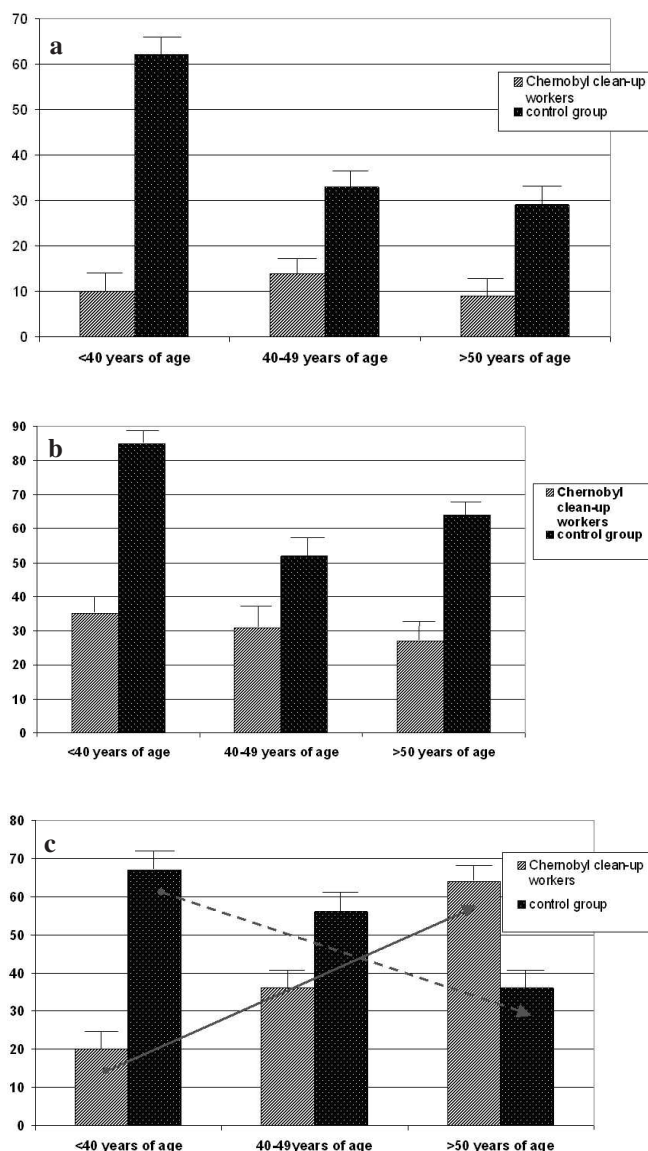


Fig. 1. a) Incidence of good ability (%) of PBL to produce interferons (100–400 IU) to NDV depending on age; b) incidence of good ability (%) of PBL to produce interferons (100–400 IU) to dsRNS depending on age; c) incidence of good ability (%) of PBL to produce interferons (100–400 IU) to PHA depending on age ( $P < 0.01$ )

clean-up workers and blood donors was not significant (Fig. 2b). More blood-donors were unable to produce IFN after induction by dsRNA in comparison with Chernobyl clean-up workers in age groups over 50 (Fig. 2c).

**The production of IL-4 as well as TNF- $\alpha$ , spontaneously as well as after stimulation by PHA or LPS in Chernobyl clean-up workers blood cells was very low and similar in all age groups. The production of TNF- $\alpha$  by LPS and PHA after 96 hours in PBMC, in Chernobyl clean-up workers was lower in comparison with blood donors, but not significantly.**

**The concentration of soluble IL-6 was significantly higher in the Chernobyl clean-up workers after 40 years of age, but the level of soluble IL-1 $\beta$  did not differ between groups.**

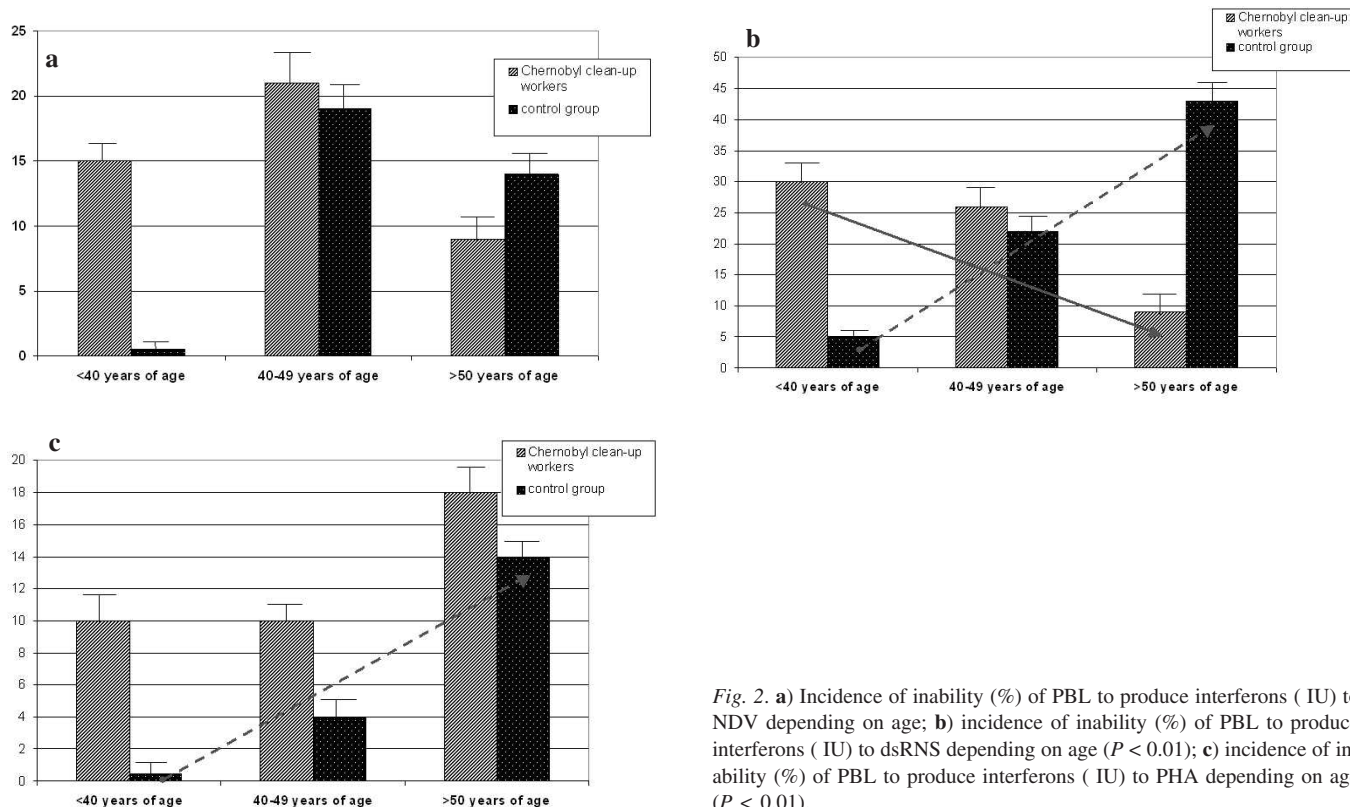


Fig. 2. a) Incidence of inability (%) of PBL to produce interferons ( IU) to NDV depending on age; b) incidence of inability (%) of PBL to produce interferons ( IU) to dsRNS depending on age ( $P < 0.01$ ); c) incidence of inability (%) of PBL to produce interferons ( IU) to PHA depending on age ( $P < 0.01$ ).

Table 1

IMMUNOLOGICAL PROFILE OF CHERNOBYL CLEAN-UP WORKERS AND DONORS DEPENDING ON AGE

Indices	Age < 40		Age 41-49		Age > 50	
	clean-up workers	donors	clean-up workers	donors	clean-up workers	donors
PBL	7,040±2,428	6,058±1,004	8,241 ±2,058*	5,269±1,402*	7,562±1,547	6,371±1,447
Ly, %	30.4±4.8*	37±5.8*	26.7±6.0	34.4±7.2	31.3±7.8	32.7±6.6
Mo, %	5.2±1.9	4.6±1.6	7.1±2.4	4.7±2.2	6.7±2.1	5.6±2.1
CD3+, %	60.8±9.3*	73.5±7.8*	70.8±8.3	70.9±9.4	72.8±13.4	69.1±11.9
CD4+, %	37.8±6.7	42.6±7.3	45.1±7.6*	39.3±7.0*	39.2±9.6	39.0±6.6
CD8+, %	25.0±11.5	30.4±7.2	25.4±6.5*	33.5±10.7*	37.2±13.3	30.1±14.2
CD16+, %	28.4±10.9*	15.0±7.1*	15.6±7.4	16.0±5.9	15.9±9.7	18.3±10.2
CD19+, %	11.6±1.3	11.4±4.2	11.8±6.1	9.7±4.4	9.0±4.1	12.4±10.0
CD25+, %	5.8±1.4*	3.1±1.2*	3.7±1.6	3.4±1.7	3.7±1.1	3.0±1.0
IgA, mg%	2.1±0.6	2.5±0.7	2.2±0.8	2.2±0.8	2.9±0.9	2.3±0.8
IgG, mg%	12.1±2.1	10.9±2.1	11.1±3.3	10.4±1.8	11.5±2.7	11.7±2.5
IgM, mg%	1.6±0.4	1.1±0.6	1.1±0.4	1.2±0.6	1.2±0.4	0.9±0.6
sIL-6, pg/ml	6.4±1.2** n=21	3.7±0.9** n=20	9.2±0.7**/*** n=19	4.2±0.9* n=22	n.d.	n.d.
sIL-1β, pg/ml	7.8±0.6 n=21	7.1±1.2 n=20	6.7±0.3 n=19	6.9±0.9 n=22	n.d.	n.d.

PBL, peripheral blood leukocytes; IgA, IgG, IgM, immunoglobulins; \* $P < 0.05$ , Chernobyl clean-up workers versus donors between age-matched groups; \*\* $P < 0.05$ , Chernobyl clean-up workers versus donors and clean-up workers between different age groups; n.d. - no data

**Comparison of cell-immunity parameters in Chernobyl clean-up workers and control groups** showed some significant differences (Table 1):

- Age < 40: Chernobyl clean-up workers had a significantly lower percentage of lymphocytes, but increased

number of CD16+ and CD25+ cells in comparison with age-matched donors;

- Age 40–49: Chernobyl clean-up workers had significantly higher number of PBL, monocytes, CD4+ cells and decreased number of CD8+ cells in comparison with the control group;



- Age > 50: Chernobyl clean-up workers had an increased number of CD8+ cells compared with donors.

## DISCUSSION

Ageing is associated with changes in most parts of the immune system (Rea *et al.*, 1996; Franceschi *et al.*, 2000; Mysliwska *et al.*, 2000; Yen *et al.*, 2000; Weksler *et al.*, 2002; Schindovski *et al.*, 2002). A causal ration between impaired immune function during ageing and increased susceptibility to infections and cancers remains to be demonstrated. Ageing is associated with chronic low-grade inflammatory activity (Franceschi *et al.*, 2000; Franceschi and Bonafe, 2003). As has been shown in several studies that the level of TNF $\alpha$ , IL-6, IL-1Ra increases with age (Bruunsgaard *et al.*, 2001). Immunosenescence is characterised by impaired cellular immunity combined with low-grade inflammation. Possible, chronic low-grade inflammatory activity may cause exhaustion of T lymphocytes through long-term activation and bystander proliferation.

An important part of human ageing is a decline in the ability of individuals to adapt to environmental stress. The hypothesis that exposure to ionising radiation accelerates the natural processes of ageing has been investigated in a population of A-bomb survivors in Japan by means of clinical, epidemiological, and laboratory methods (Sasaki *et al.*, 1991). Immunological changes among A-bomb survivors in PHA response and mixed lymphocyte culture response showed equivocal radiation effects. The frequency of T lymphocyte TCR mutation increased with age and also with radiation dose (Sasaki *et al.*, 1991). Chumak *et al.* (2001) suggested that early ageing of the immune system was a result of radiation exposure. The immunological reactions of the heavily irradiated Chernobyl accident victims and clean-up workers differed during the period of the acute radiation syndrome and during the recovery period. In the recovery period inhibition of immune function remained; this was associated with changes in lymphocyte subsets, such as decreased CD3+ and CD4+ T-lymphocyte counts and increased numbers of somatic mutations at the T-cell receptor locus (Chumak *et al.*, 2001).

T cells, which are central to the correct functioning of the immune system, decline with age due to thymus involution (Aspinall and Andrew, 2000). A significantly decreased number of total T lymphocytes in CD3 and in the CD4 and CD8 subsets was observed in aged humans by Schindovski *et al.* (2002). A lack of T cells may be one of the numerous causes of immunosenescence, since fewer cells providing immune function are available to maintain immune homeostasis. Age-related impaired T cell function is associated with increased mortality risk.

In our study, we did not observe any significant age-related changes in cell subsets in control groups, which supports some previous studies (Yen *et al.*, 2000). In Chernobyl clean-up workers the number of CD8+ cells increased, but

the number of CD25+ cells gradually decreased with age. Possibly, the lack of differences in T-cell subsets between the investigated age-related groups in the control group in the current study could be explained by the chosen groups for investigation, i.e. the age differences were not large enough. Nerlan *et al.* (2002) as well as Franceschi *et al.* (2000) reported an increase of IL-6 and TNF- $\alpha$  production by T cells in peripheral blood in elderly subjects that could be due to basal inflammation by age. TNF- $\alpha$ , a proinflammatory cytokine, has a central role in the stimulation of cellular and inflammatory reactions. Fagiolo and Toriani-Terenzi (2002) observed high TNF- $\alpha$  levels both in lipopolysaccharide stimulated and unstimulated blood mononuclear cells after irradiation. Our obtained data did not show any change in TNF- $\alpha$  production in Chernobyl clean-up workers. Regarding IFNs, previous experimental investigations of IFN- $\gamma$  production show opposite effects depending on age and/or irradiation: increased as well as decreased level of interferon (Ганова *и др.*, 1994; Алимбарова *и др.*, 1997; Zhang *et al.*, 2000; Zhang *et al.*, 2002; Griffin *et al.*, 2006). The evaluation of the interferon status of children living in areas with increased radiation background revealed a reduced capacity of blood lymphocytes to produce gamma-interferon as well as an increased level of circulating interferon in serum (Алимбарова *и др.*, 1997). The results of our study showed a decreased IFNs common production in the liquidators from Latvia 15 years after the Chernobyl disaster. However, the incidence of good ability of peripheral blood leukocytes to produce IFNs induced by PHA mitogen significantly increased with age in Chernobyl clean-up workers.

Natural killer lymphocytes are considered to be involved in immunosurveillance against tumours and in viral defence. Their age-related changes in activity are still controversially discussed in the literature (Mysliwska *et al.*, 2000; Schindovski *et al.*, 2002), but most studies show increased number and activity of NK cells with advancing age. In contrast, irradiation has an inhibitory effect on human NK activity (Fuggetta *et al.*, 1998). In our study a significant correlation with age in the percentage of NK cells was found in Chernobyl clean-up workers — the number of NK cells gradually decreased whereas in the control group we did not observe any changes with age.

On the other hand, Burns *et al.* (1993) reported that a decline of immune function with age is due to impaired B cells function but is not restricted to T lymphocytes (Burns *et al.*, 1993). However, defective T helper activity might contribute to an altered B cell functionality and could account for one aspect of the altered humoral activity associated with age (Burns *et al.*, 1997). The age-associated decrease in the antibody response to foreign antigens suggests that immune senescence leads to the most common immunodeficiency state or dysregulation (Weksler *et al.*, 2002). The number of blood B cells secreting immunoglobulins was observed to increase with age but the serum concentration of the immunoglobulins did not decrease with age (Weksler *et al.*, 2002). Possibly, the basis for age-associated

polyclonal B cell activation depends on the increased production of IL-4 and IL-6 production by T cells in the elderly. In our study we did not observe any changes in immunoglobulin production in Chernobyl clean-up workers or in control groups.

In conclusion, we found that the concentration of pro-inflammation cytokine sIL-6 in peripheral blood as well as the ability of PBL to produce IFNs after PHA stimulation in 24 h in Chernobyl clean-up workers from Latvia were correlated with age. We suggest that ongoing ageing processes are reflected by the induction of IFNs of leukocytes in both examined groups: in Chernobyl clean-up workers as well as in donors. However, the character of the production differs: increases in clean-up workers with age, but decreases in donors. The increased plasma levels of soluble IL-6 might be the consequence of an age-dependent inflammatory reaction in Chernobyl clean-up workers as well as of the presented incorporated radionuclides.

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## NOVECOŠANĀS UN CITOKĪNU SINTĒZE ČERNOBIĻAS AVĀRIJAS SEKU LIKVIDĒTĀJIEM NO LATVIJAS

Šobrīd pasaulē vērojama padziļināta interese par priekšlaicīgas novecošanās patoģenēzi. Mūsdienu vienotās novecošanas teorija atzīst, ka visraksturīgākais novecošanās procesam ir progresīvi pieaugošs proiekaisuma stāvoklis, kas pavada adaptācijas mazspēju. Vispārzināms ir fakts, ka jonizējošā radiācija paaugstina audu novecošanos. Radiācijas izraisītā audu bojājuma sekas ir iekaisums, kurā iesaistās citokīni – signālpolipeptīdi, ko izstrādā galvenokārt imūnās sistēmas aktivētās šūnas. Radiācijas izraisītā iekaisumā, kas var būt gan akūts, gan hronisks, piedalās pro-iekaisuma citokīni: IL-6, IL-1 $\alpha$ , IL-1 $\beta$ , TNF- $\alpha$  un citi. Nepārtrauktā iekaisuma stimulu klātbūtne veido bioloģisko pamatu paaugstinātai predispozīcijai attiecībā pret t.s. vecuma slimībām un paaugstina risku saslimt ar ļaundabīgiem audzējiem. Černobiļas avārijas seku likvidētāji, kuri savulaik bija pakļauti relatīvi īslaicīgam ārējām apstarojumam un visu atlikušo dzīvi ir inkorporēto radionuklīdu „nēsātāji”, no zinātniskās izpētes viedokļa ir interesanta grupa, tai skaitā attiecībā uz novecošanās procesa dinamiku saistībā ar proiekaisuma citokīnu līmeņa pārmaiņām. Sakarā ar to, ka ik gadus pasaules vispārējais radiācijas fons pieaug, jautājums pārsniedz vien tikai „Černobiļas” ietvarus. Mūsu darba mērķis bija novērtēt dažu citokīnu (interferonu, IL-1 $\beta$ , IL-4, IL-6, TNF- $\alpha$ ) sintēzi Černobiļas avārijas seku likvidētājiem atkarībā no vecuma salīdzinājumā ar atbilstoša vecuma vīriešiem, kuriem nav bijusi profesionāla saskarsme ar jonizējošo radiāciju (kontroles grupu). Pētījums veikts Arodslimību un staru patoloģijas centrā VAS Paula Stradiņa KUS 2001.–2003. gadā. Kopumā izmeklēti 113 Černobiļas avārijas seku likvidētāji, kas 1986. gada maijā piedalījušies avārijas seku likvidācijas darbos un 103 atbilstoša vecuma un dzimuma Latvijas iedzīvotāji, kas netika pakļauti radiācijas darbībai (kontroles grupa). Personas tika sadalītas trijās dažāda vecuma grupās: (< 40 gadi; 40–49 gadi; > 50 gadi). sIL-1 $\beta$  un sIL-6 citokīnu līmenis tika noteikts asins plazmā 42 likvidētājiem un 40 donoriem. Citokīnu IL-2, IL-4 un TNF- $\alpha$  spontāna indukcija un ar mitogēniem fitohemaglutinīnu (PHA) un lipopolisaharīdu (LPS) stimulēta ierosa izmeklējamu personu perifēro asiņu mononukleāro šūnu kultūrās tika vērtēta pēc 24 un 96 stundām. Perifēro asiņu leukocītu spēja ražot interferonus pēc to *in vitro* indukcijas ar trim dažādiem induktoriem: fitohemaglutinīnu, Ņūkāstlas slimības vīrusu un divpavedienu RNS tika pētīta 73 Černobiļas avārijas seku likvidētājiem un 63 donoriem. Rezultātus noteicām, titrējot ar vīrusu citopātiskās inhibīcijas standarta metodi pārprotējamo audu kultūrā L-41, kā testa vīrusu izmantojot encefalomiokardīta vīrusu. Interferonu sintēze visiem Černobiļas avārijas seku likvidētājiem bija samazināta, salīdzinot ar kontroles grupu. Tomēr likvidētāju grupā fitohemaglutinīna-inducēta interferonu veidošanās (pēc 24 st.) palielinās tieši proporcionāli vecumam, bet kontroles grupā – otrādi, samazinās. sIL-6 koncentrācija bija statistiski ticami augstāka likvidētāju grupā pēc 40 gadiem. TNF- $\alpha$  un IL-4 indukcija neatšķiras starp Černobiļas avārijas seku likvidētājiem un donoriem. Iegūtie dati var liecināt par interferonu sistēmas piedalīšanos ar vecumu nosacīta iekaisuma procesā: Černobiļas avārijas seku likvidētājiem ar vecumu pieaug, bet donoriem – samazinās. Paaugstināta sIL-6 pro-iekaisuma citokīna koncentrācija perifērajās asinīs Černobiļas avārijas seku likvidētājiem var norādīt uz iekaisuma procesu organismā inkorporēto radionuklīdu esamības vai arī dabīgas novecošanas dēļ.