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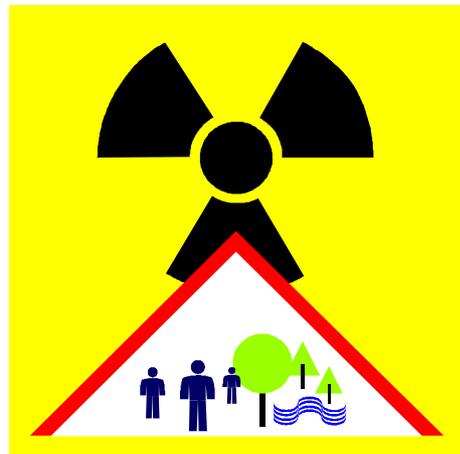
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Radiation Protection 121

Thyroid diseases and exposure to ionising radiation: Lessons learned following the Chernobyl accident Proceedings of the scientific seminar held in Luxembourg on 26 November 1998

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Environment

CONTENTS

FOREWORD

One of the consequences of the Chernobyl accident has been an increase in the incidence of thyroid cancers in the exposed population and particularly in children. The European Commission organised the seminar on thyroid diseases in response to a wish of the members of the Group of experts referred to in Article 31 of the Euratom Treaty to discuss in depth this particular aspect of the consequences of the Chernobyl accident.

Under the terms of the Treaty establishing the European Atomic Energy Community, the Community shall, amongst other things, establish uniform safety standards to protect the health of workers and of the general public against the dangers arriving from ionising radiation. The most recent version of such standards is contained in the Council Directive 96/29/Euratom of 13 May 1996 laying down basic safety standards for the protection of the health of the workers and the general public against the dangers arising from ionising radiation.

The standards are approved by the Council, on a proposal from the Commission, established taking into account the opinion of the Group of experts referred to in Article 31 of the Treaty.

The aim of the seminar was to present elements for assessing whether the above-mentioned Directive continues to ensure an adequate level of protection at the light of the recent information gathered following the Chernobyl accident.

Leading scientists participating in the European research and training programmes presented the latest developments on the subject, notably following the scientific seminars organised by the main International Organisations in 1996 and 1997, ten years after the accident.

GENETIC AND ENVIRONMENTAL FACTORS INFLUENCING THE RADIATION-INDUCED CANCER RISK

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INTRODUCTION

Thyroid cancer is one of the least frequent causes of death from cancer. In the general population, it accounts for approximately 1% of the total cancer incidence. The association between thyroid cancer and exposure to ionizing radiation was suggested in 1950 {1} and has been well studied in epidemiological of exposed populations, A number of other risk factors have also been suggested, supported by clinical or screening series, but these have been formally studied only in relatively few systematic epidemiological studies and their possible role in radiation induced thyroid cancer has not typically been examined rigorously.

The accident, which occurred in reactor 4 of the Chernobyl power plant in Ukraine in April 1986, resulted in widespread radioactive contamination on the territories of Belarus, Russia and Ukraine. The main radionuclides were ^{137}Cs and ^{131}I; exposure to short-lived isotopes of iodine also occurred in the first hours and days following the accident. In Belarus, it is estimated that several hundreds of children received thyroid doses from ^{131}I of the order of 10 Sv or more {2, 3} and are thus at increased risk of radiation induced thyroid cancer. The extremely large increase in the incidence of a thyroid cancer in children in areas contaminated by the Chernobyl accident suggests important hypotheses concerning factors which may modify the association between radiation dose and thyroid cancer risk.

1.   PREDICTIONS OF RISK

We have made predictions of radiation induced thyroid cancer risk over life – as well as over the first 10 years after the accident for populations of Belarussian and Russian children exposed before the age of 5 — using age- and sex-specific thyroid cancer rates from England and Wales as baseline and age- and sex-specific mortality rates for the period 1986-90 and 1992-93 for Belarus {4}. Table 1 shows the number of cases predicted using the radiation risk estimates from Ron and collaborators {5}. Three alternatives were used: model 1 corresponds to a constant ERR of 7.7 per Gy over life; model 2 to the same ERR over 40 years; model 3 to the constant ERR model over life with sex and time since exposure modifiers. The spontaneous number of cases corresponds to the numbers of cases expected in these populations in the absence of an effect of exposure from the accident.

Table 1. Number of cases predicted from RR estimates of Ron et al {5} *(children 0-4 at exposure) (Table reproduced from Cardis et al {4})*

Age at exposure	Populat. in 1986	Dose[1] (Gy)	First 10 years Cases	Life time Sponta neous cases	Model 1 Cases	Model 1 *AF%[2]*	Model 2 Cases	Model 2 AF%	Model 3 Cases	Model 3 AF%
Gomel										
<1	28 888	1.30	0.6	26	293	*91*	97	*74*	258	90
1-3	85 341	1.23	3.8	80	837	*91*	319	*75*	761	89
4	26 839	0.97	1.2	25	212	*88*	87	*72*	194	87
0-4	141 068		5.6	131	1 342	*90*	503	*74*	1213	89
Mogilev										
<1	20 661	0.61	0.2	19	109	*83*	44	*57*	97	80
1-3	60 927	0.42	1.1	57	245	*77*	116	*51*	222	74
4	19 358	0.35	0.4	18	68	*74*	34	*47*	62	71
0-4	100 946		1.7	94	422	*78*	194	*52*	381	75
Russia (Kaluga+Tula+Orel)										
0-4	247 899	0.06	1.4	234	333	*30*	275	*15*	291	20

2. NUMBER OF CASES OBSERVED IN 1987-1997 IN BELARUS AND RUSSIA

The dramatic increase in thyroid cancer observed, following the Chernobyl accident, among those who were children at the time and lived in territories contaminated by fallout from the accident has been well documented. All cases of thyroid carcinoma diagnosed between 1987 and 1997 in Belarus and in three contaminated regions of Russia (Kaluga, Orel and Tula) among children are presented in Table 2 {4}. They were

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[1]Average thyroid dose from ^{131}I in this age group in the most contaminated districts of the region – note: this is likely to be a substantial overestimation of the average dose in the region

[2] AF%: attributable fraction %: percentage of total number of predicted cases attributed to the radiation exposure

identified through cross-checking of cancer registries and records of medical institutions where the cases were diagnosed and treated. It is notable that the numbers actually observed up till now are very big (respectively 157, 16 and 21 for Gomel, Mogilev and the three regions of Russia), compared to the total number of cases predicted in the first 10 years after the accident (5.6, 1.7 and 1.4), particularly in Gomel.

Table 2. Number of cases observed in 1987-1997, by age at accident and region *(Table reproduced from Cardis et al {4})*

		Belarus		Russia
	Whole	*Gomel*	*Mogilev*	3 oblasts
0-4	323	*157*	*16*	21
5-14	270	*108*	*15*	58
Total	593	*265*	*31*	79

3. POSSIBLE REASONS FOR INCREASE

The number of cases observed to date is much greater, particularly in the Gomel area, than that which we would have been expected over 10 years, based on the experience of other populations exposed as children.

The reasons for discrepancies between the numbers of predicted and observed cases could be various:

- Doses could be greatly underestimated. However, the dose estimates used in the predictions shown above are likely to be too high (measurements in contaminated districts have been used for whole oblast).
- Other short-lived isotopes of iodine may have been deposited in areas affected by rainfall. Little is known about the carcinogenic potential of isotopes of iodine other than [131]I. Exposure has occurred among Marshall Islanders but epidemiological and experimental studies to date do not permit a conclusive evaluation of their carcinogenic potential.
- The effect of screening for thyroid cancer may play a role because a considerable amount of screening for thyroid disease has taken place in the contaminated regions of Belarus and Russia. The effect of screening on the incidence of thyroid cancer can be very important – resulting in up to 10 fold increases of incidence {13}{ICRP (International Commission on Radiological Protection) 1991 ID: 41}. Screening can also change the apparent pattern of risk over time – by advancing the detection time of tumours. It is difficult to evaluate the effect of screening in young people, as little information is available on occult tumours of children and adolescents.

Another possible reason for the discrepancy may be the existence of factors — either environmental (iodine status) or host (age at exposure, sex, genetic predisposition) — which modify the risk of radiation induced thyroid cancer. Current evidence for the role of such factors in radiation induced thyroid carcinogenesis is reviewed below.

4. MODIFYING FACTORS

4.1. Familial occurrence

Although the majority of PTC's are sporadic tumours, there is evidence for familiarity of PTC. A number of family and epidemiological studies have raised the hypothesis, particularly following radiation exposure {14, 15}.

Two familial cancer syndromes that include thyroid cancer of follicular origin – Gardner's syndrome and Cowden's disease – support the existence of genetic factors in the etiology of thyroid carcinoma. Familial aggregation in families with no evidence for these syndrome was reported in the US {16}, in a high risk area of Norway {17} and other countries, suggesting that genetic factors may be important determinants for the geographic distribution of the disease {18-20}. More recent study of two families in Tasmania in {21} showed evidence of autosomal dominant inheritance of PTC associated with multinodular goiter.

The association of non-medullary carcinoma of the thyroid and parental cancer was tested formally in a population based case-control study in Sweden {22}. The study considered the history of cancer among parents of 517 histologically confirmed cases of papillary and follicular carcinoma and a similar number of sex- and age-matched controls. Maternal history of cancer was more common among women with follicular carcinoma than among their controls. Among the cohort of parents of thyroid cancer cases, parents of probands with papillary carcinoma had an increased risk of thyroid cancer (odds ration (OR) 4.25, 95% confidence interval (CI) 1.16-10.89) compared to the general population. Although the effects of shared environmental exposures and of increased medical screening in families with one thyroid cancer cannot be ruled out, the association found between the NMC of the thyroid and parental cancer is relatively strong and lends strength to the hypothesis of genetic predisposition to thyroid cancer.

There is evidence of familial aggregation in both irradiated and unirradiated populations {22-30}.

In recent years, a number of morphological subtypes of thyroid tumors derived from the follicular cell have been identified that can be shown to occur in families, thus indicating an inherited predisposition to the development of these particular types of tumor {31-33}. Exposure to a mutagen, such as radiation, would be predicted to increase the frequency of such familial tumors. Four groups have so far been identified:

- Dishormogenesis: Thyroid tumours may develop in patients who have a rare congenital deficiency in one of the steps of thyroid hormonogenesis (commonly either a defect in thyroglobulin or thyroid peroxidase which results in decreased T3 and T4 production).
- Familial polyposis coli (FAP) associated thyroid tumours: Thyroid tumours of an unusual morphology are observed occasionally in patients who are heterozygous for mutation in the apc gene. Germline heterozygosity for loss of function of this gene results in the development of multiple colonic polyps, some of which progress to colonic neoplasia. Multiple thyroid tumours have been observed in a few patients with FAP.
- Familial Oxyphil Tumours

- Multiple benign papilloid adenomas

It is notable that, among the cases, which we studied in Belarus and Russia, 10 families were found in which two siblings were affected. Given the rarity of this disease in children, this observation strengthens the assumption that genetic predisposition – perhaps related to ethnic origin – may be increasing the susceptibility to radiation induced thyroid cancer.

4.2. Age at exposure

Age at exposure is the only established modifying factor for radiation induced thyroid cancer {6}. The risk of radiation induced cancer is considerably greater in those exposed as young children than as adults {6}, with excess relative risks (ERR) for external irradiation before the age of 20 ranging from 2.1 to 17 per Gy. There is some evidence that radiation may increase slightly the aggressiveness of childhood tumours {34}.

In studies of atomic bomb survivors and of children exposed to ionizing radiation for tinea capitis {35} and other benign disorders, the major increased risk is observed ten years or more after exposure and does not appear to decrease with time thereafter. There is little data from other studies on children who were very young at the time of exposure, and it is possible that the risk in these is even higher than previously estimated and that the pattern of risk over time differs from a constant relative risk model.

4.3. Iodine deficiency and iodine intake

Experimental studies have shown that excessive long-term stimulation of the thyroid gland by thyroid stimulating hormone (TSH), such as results from iodine deficiency, can lead to tumour formation with or without addition of a mutagenic agent {36}. Animal experiments indicate that iodine deficiency is a potent promoter of thyroid carcinogenesis {37, 38}. Studies also indicate that iodine excess may play a role in tumour promotion in experimental animals {39}.

In humans, opinions differ on this point, since the observations often yield contradictory results. The highest incidence of thyroid carcinoma is seen in Iceland and Hawaii {40}, both areas with a high iodine intake.

A significant elevation in the prevalence of follicular and anaplastic, but not papillary thyroid carcinoma was seen in an iodine deficient area of Northeastern Sicily compared to a control area in a population-based survey {41}.

Studies of a number of human populations have shown that iodine supplementation added to a population's diet in an iodine-deficient area causes the prevalence of papillary thyroid carcinoma to rise, whereas the prevalence of follicular and anaplastic thyroid cancer declines {42}.

Some studies have showed an association between a prior history of goiter or benign nodules and risk of thyroid cancer {15, 23, 29, 43, 44, 45, 46}.

More recently, in a population based case-control study in Sweden {47}, although no association was seen between residence in areas of endemic goiter and risk of thyroid cancer overall, associations were seen with duration and age at first residence in these areas. For follicular carcinoma, the association was strongest for residence for 21 to 40 years, particularly for cases diagnosed before the age of 50. For papillary carcinoma, the

temporal relation was more complicated; exposure for the first time during adolescence was associated with an increased risk, particularly among women. This observation could be explained by the effect of hyperstimulation of the thyroid concurrent with a sudden rise in female endogenous sex hormones at puberty.

In a population based study of regional patterns of thyroid cancer in relation to iodine intake and iodination in Sweden, residence in iodine-deficient regions was associated with a 2-fold increased risk of follicular cancer in men and a 17% increase in women {48}. The relative risks for PTC and anaplastic carcinoma in this study were 0.80 and 0.87 respectively. Following introduction of iodination (of salt and milk), the prevalence of goiter diminished as expected, while the incidence of follicular carcinoma increased, particularly in previously iodine deficient areas. The incidence of papillary thyroid carcinoma, however, increased steeply, both in iodine deficient and in iodine sufficient areas, suggesting the increase was unrelated to iodine supplementation.

Epidemiological studies in China, Hawaii and Norway have found an increase in thyroid cancer associated with high iodine intake from seafood {27, 44, 49}, whereas Italian study suggested that high intake of fish conferred a significant protection {50}.

The relation between iodine intake and risk of thyroid cancer appears to be complex, since both iodine deficiency and iodine excess may inhibit the synthesis of thyroid hormones and cause goiter. It is possible that the two main types of thyroid carcinoma (papillary and follicular) are linked to iodine rich and iodine deficient diets, respectively, although this is not apparent from the studies reviewed above.

A number of authors {51, 52, 53} have indicated that some of the contaminated areas of Belarus and Russia were (and continue to be) areas of moderate iodine deficiency. As indicated above, iodine deficiency could be an important modifier of the risk of radiation induced thyroid cancer in the three affected countries. However, there is no available literature to the date on the joint effects of radiation and iodine deficiency in the induction of thyroid cancer in humans.

4.4. Hormonal and reproductive factors

Thyroid cancer occurs more frequently in women (about three times more than in men), suggesting that hormonal factors play a role in its etiology.

Several epidemiological studies have considered the role of reproductive history – including age at menarche, age at first pregnancy, parity, age at menopause – in thyroid carcinogenesis. An association between parity and risk of thyroid cancer was observed in a case-control study in Connecticut {23} and, among young women, in a study in California {29} and Shanghai {44}. This is supported by findings of two additional studies {26, 54}, but not by those in Hawaii {27} or in Sweden and Norway {55}. In the later study, however, an increased risk was seen for a first childbirth before the age of 20 and for women with a history of artificial menopause.

Several studies have also shown an association between miscarriage and/or abortion and the risk of thyroid cancer {44, 23, 27, 45}. An association between mothers' miscarriage and subsequent risk of thyroid cancer daughters was also reported {56}.

Little is known about the effect of hormonal factors in radiation induced thyroid cancer. However, if thyroid stimulation at menarche and during pregnancy increases the risk of

thyroid cancer in general, it is likely that it also plays a role in the expression of radiation induced thyroid cancer. This hypothesis is supported by the observation that all thyroid cancers in the exposed Marshall Islanders occurred in multiparous women. A recent case-control study suggested that parity potentiated the radiation-induced risk of thyroid cancer {23}. If this is so, young women who were children at the time of the Chernobyl accident may have an even greater increased risk as they become young adults and start to have children.

4.5. Diet

In addition to the iodine content of the diet mentioned above, a number of other factors might play a role in thyroid carcinogenesis. Animal data on the joint effects of goitrogens and ionizing radiation show a synergistic relationship between the two {7}, but almost no information is available for humans. The more general question of whether dietary consumption of goitrogens increases thyroid cancer risk has been addressed in several studies. Cruciferous vegetables contain relatively high levels of chemicals that endogenously degrade to thiocyanates, which block iodine activity and can also modify the interaction of thyroid hormones with their serum binding protein {50}. There is substantial overlap between goitrogenic and cruciferous vegetables, and the later category also has been noted to contain a variety of constituents that can inhibit carcinogenesis {57}.

Consumption of cruciferous vegetables was associated with a reduced risk of thyroid cancer in two studies {23, 28}. There was also found limited evidence of a protective effect for goitrogenic vegetables only in females in Hawaii study {27}. In another study, in Sweden and Norway, an association with these vegetables was seen only in persons who lived in areas of endemic goiter {58}. The role of goitrogens may be important in the regions contaminated by the Chernobyl accident, because vegetables containing goitrogens (i.e. cabbage) represent an essential source of calories in Russia and Belarus and coexist with iodine deficiency.

A positive association was found between current consumption of butter and cheese and risk of thyroid cancer in a study in Sweden and Norway {58}, as well as in a study in Northern Italy and in a pooled analysis of four case-control studies {28, 50}.

Fruit consumption was associated with a reduced risk of thyroid cancer in two studies {28, 50}, while inconsistent results were seen in the Swedish and Norwegian study {58}.

The association between alcohol intake and risk of thyroid cancer is unclear; associations were observed in one study in Italy {28}, but not in three studies in the US and Nordic countries, where alcohol consumption on average is less than in Italy {23, 27, 58}.

Effects of dietary changes from adolescence to adult life were observed in the Swedish/Norwegian study, compatible with the hypothesis that iodine deficiency in the peripuberal period is associated with thyroid cancer risk {58}.

4.6. Other factors

Many studies have considered the possibility that thyroid cancer is preceded by other thyroid abnormalities, including goiter, benign thyroid nodules and thyroiditis. Several case-control studies of thyroid cancer have reported an association between pre-existing benign thyroid nodules and goiter and thyroid cancer {15, 23, 27, 28, 29, 44}. In a case-

control study in California, an association was also found with family history of thyroid cancer or other thyroid disease {56}. These diseases, however, are common, and most studies have been inconclusive, in particular because ascertainment of thyroid cancer among persons with pre-existing thyroid diseases may be greater than in a general population.

5. CONCLUSIONS

The current paper has reviewed the current status of our knowledge concerning modifying factors for radiation induced thyroid cancer. Our analyses of the data from Belarus and Russia indicates that the observed thyroid cancer increase following the Chernobyl accident is much greater and may have greater public health consequences than predicted from the experience of other populations.

This raises the important public health and radiation protection hypothesis that the incidence of thyroid cancer following the Chernobyl accident is either increased or accelerated due to the presence of factors – either environmental or host – which modify the relation between radiation exposure and subsequent thyroid cancer risk. *At present, however, only hypotheses can be raised and further work is needed before lessons can be drawn to inform the setting of safety standards.*

Therefore, the following actions are needed.

1. *Public health actions* to prevent or limit the radiological consequences of the accident in the contaminated territories, including iodine supplementation of the diet of populations residing in iodine deficient areas and recommendations on the dietary habits, focused screening of the "highest risk groups": those who were very young at the time of the accident, who lived in the most contaminated areas, the young girls starting the age of menarche and having children.

2. *Research*:
   It is necessary to continue monitoring of rates in the contaminated areas to further elucidate the effects of the accident. This will allow better planning of public health actions. It will also allow the characterization of the pattern of risk over time and thus help make better predictions in the case of future accidents for the purpose of radiation protection.

   The increase in thyroid cancer following the Chernobyl accident is a unique opportunity to learn about possible modifying factors for radiation induced thyroid cancer. Finding a genetic predisposition or elucidating the role of iodine deficiency and of reproductive factors will have important implications both for radiation protection of patients and the general population in the case of future accidents. It will also allow more focused public health actions among exposed populations, helping to further identify the high-risk groups, which need to be screened.

   A study of these modifying factors is currently underway in Belarus and Russia. This study is partially supported until early 2000, by the Nuclear Fission Safety Programme of the European Community and the Sasakawa Memorial Health Foundation of Japan.

References

1. Duffy, B., Fitzgerald. Thyroid cancer in childhood and adolescence. Report of 28 cases. *J. Clin. Endocrinol. Metab.* 1950; **10**: 1296-1308.
2. L.A. Ilyin, M.I. Balonov, L.A. Buldakov et al., Radiocontamination patterns and possible health consequences of the accident at the Chernobyl nuclear power station. *J. Radiol. Prot.* 1990; **10**: 3-29.
3. International Chernobyl Project, *Assessment of radiological consequences and evaluation of protective measures. Technical Report.* International Atomic Energy Agency, Vienna 1992.
4. Cardis, E., Amoros, E., Kesminiene, A., Malakhova, I., Polyakov, S., Piliptsevich, N., Demidchik, E., Astakhova, L., Ivanov, V., Konogorov, A., Parshkov, E., Tsyb. A. Observed and predicted thyroid cancer incidence following the Chernobyl accident - evidence for factors influencing susceptibility to radiation induced thyroid cancer. Proceedings on International Symposium on Radiation and Thyroid Cancer. Cambridge, July 20-23, 1998. *(In press).*
5. Ron, E, Lubin, J, Shore, RE, Mabuchi, K, Modan, B, Pottern, LM, Schneider, AB, Tucker, MA, Boice, JD, Jr. Thyroid cancer after exposure to external radiation: a pooled analysis of seven studies. *Radiat Res* 1995; **141**: 259-277.
6. Shore, RE. Issues and epidemiological evidence regarding radiation-induced thyroid cancer. *Radiat Res* 1992; **131**: 98-111.
7. Doniachi, I. Effects including carcinogenesis of I-131 and x rays on the thyroid of experimental animals - a review. *Health Phys* 1963; **9**: 1357-1362.
8. Holm, LE, Wiklund, KE, Lundell, GE, Bergman, NA, Bjelkengren, G, Cederquist, ES, Ericsson, UBC, Larsson, LG, Lidberg, ME, Lindberg, RS, Wicklund, HV, Boice, JD, Jr. Thyroid Cancer After Diagnostic Dose of Iodine-131: A Retrospective Cohort Study. *J Natl Cancer Inst* 1988; **80**: 1132-1138.
9. Hamilton, P. M., Chiacchierini, R. P., and Kaczmarek, R. Follow-up of Persons who had Iodine-131 and Other Diagnostic Procedures during Childhood and Adolescence. 37. 1989. Rockville, MD., CDRH-Food & Drug Administration.
10. Rallison, ML, Lotz, T, Bishop, M, Divine, W, Haywood, K, Lyon, J, Stevens, W .Cohort study of thyroid disease near the Nevada test site: a preliminary report. *Health Phys* 1990; **59**: 739-746.
11. Robbins, J. and Adams, W. Radiation effects in the Marshall Islands. In: Radiation and the Thyroid, pp. 11-24, Amsterdam: Excerpta Medica. 1989.
12. Lee,W.; Chiacchierini,R.P.; Shleien,B.; Telles,N.C. Thyroid tumors following 131I or localized X irradiation to the thyroid and pituitary glands in rats. *Radiat. Res.* 1982; **90**: 307-319.
13. Schneider, A et al. Dose-response relationships for radiation induced thyroid cancer and thyroid nodules: evidence for the prolonged effects of radiation on the thyroid. *J Clin Endocrinol Metab* 1993;362-369.
14. Goldgar, DE, Easton, DF, Cannon-Albright, LA, Skolnick, MH. Systematic population-based assessment of cancer risk in first- degree relatives of cancer probands. *J Natl Cancer Inst* 1994; **86**: 1600-1608.
15. McTiernan, A, Weiss, N, Daling, J. Incidence of thyroid cancer in women in relation to previous exposure to radiation therapy and history of thyroid disease. *J Natl Cancer Inst* 1984; **73**: 575-581.
16. Phade, VR, Lawrence, WR, Martin H.M. Familial Papillary Carcinoma of the Thyroid. *Arch Surg* 1981; **116**: 836-837.

17. Lote, K, Andersen, K, Nordal, E, Brennhovd, IO. Familial occurrence of papillary thyroid carcinoma. *Cancer* 1981; **46**: 1291-1294.
18. Stoffer, SS, Van Dyke, D, Bach, EA. Familial papillary carcinoma of the thyroid. *Am J Hum Genet* 1986; **25**: 775.
19. Hrafnkelsson, J, Tulinius, H, Jonasson, JG, Olafsdottir, GSH .Papillary thyroid carcinoma in Iceland: a study of the occurrence of families and the coexistence of other primary tumours. *Acta Oncol* 1989; **28**: 785-788.
20. Kwok, CG, McDougall, IR. Familial differentiated carcinoma of the thyroid: report of five pairs of siblings. *Thyroid* 1995; **5**: 395-397.
21. Burgess, JR.; Duffield, A., Wilkinson SJ., Ware, R, Greenaway, TM, Percival, J, Hoffman, L. Two families with an autosomal dominant inheritance pattern for papillary carcinoma of the thyroid. *J. Clin. Endocrinol. Metab.* 1997; **82:** 345-8.
22. Galanti, MR, Ekbom, A, Grimelius, L, Yuen, J. Parental cancer and risk of papillary and follicular thyroid carcinoma. *Br J Cancer* 1997; **75**: 451-456.
23. Ron, E, Kleinerman, RA, Boice, JDJ, LiVolsi, VA, Flannery, JT, Fraumeni, JFJ. A population-based case-control study of thyroid cancer. *J Natl Cancer Inst* 1987; **79** : 1.
24. Schneider, A, Shore-Freedman, E, Weinstein, R. Radiation-induced thyroid and other head and neck tumours: Occurrence of multiple tumors and analysis of risk factors. *J Clin Endocrinol Metab* 1986; **63**: 112.
25. Perkel, VS, Gail, MH, Lubin, J, Pee, DY, Weinstein, R, Shore-Freedman, E, Schneider, AB. Radiation-induced thyroid neoplasms: evidence for familial susceptibility factors. *J Clin Endocrinol Metab* 1988; **66**: 1316-1322.
26. McTiernan, A, Weiss, NS, Daling, J. Incidence of thyroid cancer in women in relation to reproductive and hormonal factors. *Am J Epidemiol* 1984; **120**: 423.
27. Kolonel, LN, Hankin, JH, Wilkens, L, Fukunaga, FH, Hinds, MW. An epidemologic study of thyroid cancer in Hawaii. *Cancer Causes Control* 1990; **1**: 223-234.
28. Franceschi, S, Fassina, A, Talamini, A, Mazzolini, S, Vianello, E, Bidoli, D, Serraino, D, La Vecchia, C. Risk factors for thyroid cancer in northern Italy. Int J Epidemiol 1989; 18: 584-584.
29. Preston-Martin, S, Bernstein, L, Pike, MC, Maldonado, AA, Henderson, BE. Thyroid cancer among young women related to prior thyroid disease and pregnancy history. *Br J Cancer* 1987; **55**: 191.
30. de Vathaire, F, Francois, P, Schweisguth, O, Oberlin, O, Lé, M. Irradiated neuroblastoma in childood as potential risk factor for subsequent thyroid tumour. *Lancet* 1988;455.
31. Harach, H.R. and Williams, E.D. Solitary, multiple and familial oxyphil tumours of the thyroid gland. J Pathol., 1997 (in press)
32. Harach, HR, Williams, GT, Williams, ED .Familial adenomatous polyposis associated with thyroid carcinoma: a distinct type of follicular cell neoplasm. *Histopathology* 1995; **24**: 549-561.
33. Williams, GH, Thomas, GA, Harach, HR, Churchward, M, van Heerden, J, Williams, ED .The apc gene is linked to structurally but not functionally differentiated thyroid tumours. *J Clin Endocrinol Invest* 1997; **20**: 106.
34. Robbins, J. Characteristics of spontaneous and radiation induced thyroid cancer in children. Conference proceeding. *Elsevier Science*, 1994; 81-87, Amsterdam
35. Ron, E, Modan, B, Preston, DL, Alfandary, E, Stovall, M, Boice, JD, Jr. Thyroid Neoplasia following low-dose radiation in childhood. *Radiat Res* 1989; **20**: 516-531.
36. Thomas, G. A. and Williams, E. D. Evidence for and possible mechanisms of non-genotoxic carcinogenesis in the rodent thyroid. Mutation Research 248(2), 357-370. 1991

37. Ohshima, M, Ward, J. Promotion of N-Methyl-N-Nitrosourea-induced thyroid tumors by iodine deficiency in F344/NCr rats. *J Natl Cancer Inst* 1984; **73**: 289-296.
38. Ohshima, M, Ward, J. Dietary iodine deficiency as a tumor promoter and carcinogen in male F344/NCr rats. *Cancer Res* 1986; **46**: 877-883.
39. Kanno, J, Onodera, H, Furuta, K, Maekawa, A, Kasuga, T, Hayashi, Y. Tumor-promoting effects of both iodine deficiency and iodine excess in the rat thyroid. *Toxicol Pathol* 1992; **20**: 226-235.
40. IARC (International Agency for Research on Cancer). Cancer Incidence in Five Continents. Volume VI. Parkin et al. IARC SP 120. Lyon: IARC, 1992..
41. Belfiore, A, La Rosa, GL, Padova, G, Sava, L, Ippolito O., Vigneri, R. The frequency of cold thyroid nodules and thyroid malignancies in patients from an iodine-deficient area. *Cancer* 1987; **60**: 3096-3102.
42. Langsteger, W, Költringer, P, Wolf, G, Dominik, K, Buchinger, W, Binter, G, Lax, S, Eber, O. The impact of geographical, clinical, dietary and radiation-induced features in epidemiology of thyroid cancer. *Eur J Cancer* 1993; **29A**: 1547-1553.
43. Cuello, C., Correa, P., Eisenberg, H. Geographic pathology of thyroid carcinoma. *Cancer.* 1969; **23**: 230-239.
44. Preston-Martin, S, Jin, F, Duda, MJ, Mack, WJ .A case-control study of thyroid cancer in women under age 55 in Shanghai (People's Republic of China). *Cancer Causes and Control* 1993; **4**: 431-440.
45. Levi, F, Franceschi, S, Gulie, C, Negri, E, La Vecchia, C. Female thyroid cancer: the role of reproductive and hormonal factors in Switzerland. *Oncology* 1993; **50**: 309-315.
46. D'Avanzo, B, La Vecchia, C, Franceschi, S, Negri, E, Talamini, A. History of thyroid diseases and subsequent thyroid cancer risk. *Cancer Epidemiol Biomarkers Prev* 1995; **4**: 193-199.
47. Galanti, MR, Sparen, P, Karlsson, A, Grimelius, L, Ekbom, A. Is residence in areas of endemic goiter a risk factor for thyroid cancer? *Int J Cancer* 1995; **61**: 615-621.
48. Pettersson, B, Coleman, MP, Ron, E, Adami, HO. Iodine supplementation in Sweden and regional trends in thyroid cancer incidence by histopathologic type. *Int J Cancer* 1996; **65**: 13-19.
49. Frich, L, Akslen, LA, Glattre, E. Increased risk of thyroid cancer among Norwegian women married to fishery workers - a retrospective cohort study. *Br J Cancer* 1997; **76**: 385-388.
50. Franceschi, S, Talamini, R, , Fassina A, Bidoli, E. Diet and epithelial cancer of the thyroid gland. Tumori 1990; 76: 331-338.
51. Gembicki, M, Stozharov, AN, Arinchin, AN, Moschik, KV, Petrenko, S, Khmara, IM, Baverstock, KF. Iodine deficiency in Belarusian children as a possible factor stimulating the irradation of the thyroid gland during the Chernobyl catastrophe. *Environ.Health Perspect.* 1997; **105:** 1487-1490.
52. Mityukova, T, Astakhova, L, Asenchyk, L, Orlov, M, Van Middlesworth, L. Urinary iodine excretion in Belarussian Children. *Eur. J. Endocrinol.* 1995; **133**: 216-217.
53. Dzerzhinsky, V, Anikina, I, Balakir, E, Demidenko, A., Dzerzhinskaya, N, Kazakevich, O. Results of examinations of the health status of children living in Gomel oblast. *Report on the 1993 Chernobyl Sasakawa project workshop.* 1993.
54. Miller, AB, Barclay, T, Choi, N., Grace, M., Wall, C., Plante, M., Howe, G., Cinader, B., Davis, F.A. Study of cancer, parity and age at first pregnancy. *J.Chronic.Dis.* 1980; **33**: 595-605.
55. Galanti, MR, Hansson, L, Lund, E, Bergström, R, Grimelius, L, Stalsberg, H, Carlsen, E, Baron, JA, Persson, I, Ekbom, A. Reproductive history and cigarette

smoking as risk factors for thyroid cancer in women: a population-based case-control study. *Cancer Epidemiol Biomarkers Prev* 1996; **5**: 425-431.

56. Paoff, K., Preston-Martin, S, Mack, WJ, Monroe, K. A case-control study of maternal risk factors for thyroid cancer in young women (California, United States). *Cancer Causes.and.Control*. 1995; **6**: 389-397.

57. Palmer, S, Bakshi, K. Diet, nutrition and cancer: interim dietary guidelines. *JNCI* 1983; **70**: 1151-1170.

58. Galanti, MR, Hansson, L, Bergström, R, Wolk, A, Hjartåker, A, Lund, E, Grimelius, L, Ekbom, A. Diet and the risk of papillary and follicular thyroid carcinoma: a population-based case-control study in Sweden and Norway. *Cancer Causes and Control* 1997; **8**: 205-214.

THYROID DOSES RECONSTRUCTION AND RISK AFTER THE CHERNOBYL ACCIDENT

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INTRODUCTION

Increase of the thyroid cancer incidence in exposed children was observed in the most contaminated areas during the last 5-8 years [2,7,14,15]. The results of recent investigation generally confirm first predictions made for the selected areas of the Ukraine in 1991 regarding expected thyroid cancer rate[19,20,30]. During twelve years elapsed from the Chernobyl accident a lot of efforts were made in Ukraine, Belarus and Russia to improve thyroid dose estimates due to ^{131}I [3-7,21,22,24,25,27,34,35]. Increased interest to this problem initiated several epidemiological studies dealing with different groups of people exposed in childhood due to the Chernobyl accident.

There are several ongoing projects regarding the consequences of the thyroid exposure after the Chernobyl accident. They include Ukrainian-American and Belorussian-American cohort studies, several projects in the framework of the European Union Program Inco-Copernicus, the Japanese Sasakawa Memorial Health Foundation project, German-Belorussian and German-Ukrainian studies, etc.

1.   DOSE RECONSTRUCTION

1.1.   Available data

Information about concentration of ^{131}I and short-lived isotopes in the environmental media and human thyroids is very limited. This is the main difficulty in the thyroid dose assessment after the Chernobyl accident. Present estimations of thyroid doses are based on:

1. ^{131}I activity measurements in thyroids.
2. ^{131}I activity measurements in milk, air and water as well as radioecological models.
3.   Correlation of the thyroid doses with ^{137}Cs depositions and locations of the settlements.
4.   Questionnaires.
5.   Atmospheric dispersion models.
6.   Different combinations of 1. - 5.

In addition, important information on meteorological conditions and the beginning of the pasture period should be taken into account in the development of the model.

¹³¹I activity measurements in the thyroids

Reliable measurements of ^{131}I concentration in the thyroids can be considered as a most important basis for the dose estimations. A number of measurements available for the analysis is presented in the Table 1.

Table 1. [131]I activity measurements in the thyroids.

Country	Total number	High quality (25-40% error)
Ukraine [5,20,22,24]: Kiev city, Kiev, Zhytomyr, Chernigov and Vinnytsa oblasts	150 000	60 000
Belarus [4]: Minsk city, Gomel and Mogilev oblasts	130 000*	10 000
Russia [35]: Bryansk and Tula oblasts	14 000**	2 000

*   - from total number of 300 000 measurements
** - additionally about 28 000 measurements are available in lower contaminated Kaluga oblast [34].

A group of screened people includes the persons of all ages in rural and urban settlements mainly within a distance of 150 - 250 km from the Chernobyl nuclear power plant. In the most cases only one single measurement was carried out for each person.

Quality and uncertainties of the activity measurements in the Ukraine were analyzed by Likhtarev et. al. [24]. About 40 % of these measurements were performed with the energy-selective devices. Almost all of the measurements in Belarus were carried out by the military device DP-5 operating in dose-rate regime of measurement [4]. A specialized spectrometric equipment was used only in approximately 2 000 measurements in Bryansk and Tula oblasts of Russia [34]. In general, measurements performed in the Ukraine are considered to be more reliable.

¹³¹I activity measurements in the environmental media.

Very few ^{131}I activity measurements in milk and air are available in the Ukraine. These data were used in dose reconstruction for the inhabitants of Kiev city [21]. Analysis of ^{131}I activity measurements in soil for the contaminated areas of Russia was presented by Pitkevich et. al. [27]. 409 spectrometric measurements of ^{131}I concentration in soil (in 52 settlements), 163 measurements of grass and 54 of milk were used for the thyroid dose reconstruction in Belarus [3].

Questionnaires and interviews

Information on individual behaviour can be applied for the estimation of individual doses. Detailed questionnaire was developed and applied for the thyroid dose reconstruction in the Ukraine [25]. 16 250 people (11 766 children up to 18 y at the time of the accident) were questioned in the most contaminated areas of the Ukraine (Table 2), including 2 394 persons with monitoring measurements of the thyroid. Additionally, information about behaviour of approximately 30 000 evacuees is available [23]. These

data form a basis for the model development for dose reconstruction based on behaviour factors.

Table 2. Distribution of interviewed people in different areas of the Ukraine

Region	Number of responses			
	All ages		Children born in 1968-1986	
	Total	With measurements	Total	With measurements
Zhytomyr oblast	3103	193	1239	83
Kiev oblast	2986	190	873	167
Kiev city	776	536	691	526
Chernigov oblast	9385	1475	8963	1466
Total	16250	2394	11766	2242

About 150 000 people were interviewed in Belarus in 1988 using a simple questionnaire containing only 5 questions about residence at the time of accident, consumption of milk, starting day of the pasture period, restriction of milk consumption and administration of stable iodine [4].

Public survey was performed in Bryansk oblast in 1987 [35]. People were mainly asked about consumption of different foodstuff and applied countermeasures. About 600 questionnaires were analyzed together with ^{131}I activity measurements in the thyroids.

Other data

Very few ^{129}I measurements in soil were performed after the Chernobyl accident. These data can be used to develop the models considering correlation between ^{129}I and ^{131}I depositions or ^{129}I deposition and the thyroid dose based on other methods.

^{137}Cs soil contamination is intensively used to develop the models for the thyroid doses reconstruction. This nuclide is easy to measure at present. Comprehensive data bases exist in the Ukraine, Russia and Belarus. However, since ^{137}Cs and ^{131}I vary sufficiently in physical and chemical characteristics, estimations based on such models are associated with large uncertainties.

1.2. Results and discussion

To reconstruct thyroid doses several population groups were considered:

- People with a short-time period of intake (evacuees or people leaving the contaminated areas shortly after the accident).
- People with a long-time period of intake (not evacuated and staying in the contaminated areas for a long time).
- People evacuated, but staying in the contaminated areas longer than 5 days.

- People exposed *in utero*.
- People from "non-contaminated" area.
- Liquidators.

These groups of people were either subjected to ^{131}I activity measurements in their thyroids or not. They could live in the settlements where such measurements were either performed or not performed. Depending on this information different methods should be applied to reconstruct their exposure. Age at exposure is also an important characteristic of the population for the dose reconstruction because of the pronounced age dependence of the thyroid doses. Depending on the availability of data individual or average doses can be estimated for the specific groups of people.

Several models were developed to reconstruct radio-iodine concentrations and conditions of exposure for different groups of population [3-7,20-22,25,27,34,35].

Individual doses

Present estimations of individual doses are based on ^{131}I activity measurements in thyroids. Similar models for the individual dose estimations were developed in the Ukraine, Russia and Belarus. These models include several assumptions:

- Deposition on the territory under consideration taken place during one single day when pasture period had already started (April 27, 1986)
- Intake for the short-time period of stay on the contaminated territories can be represented by a single intake function and for the long-time period - by the time-dependence of milk contamination.
- Reference anatomical, metabolic and radioecological parameters are used.

Intake for the long-time period in Bryansk oblast is assumed to be a constant during 10-20 days after the deposition (15 in average) [35]. Then intake exponentially decreases according to the milk constant rate. Such model indirectly takes into account contribution of inhalation during the first days after the accident and possible prolonged deposition.
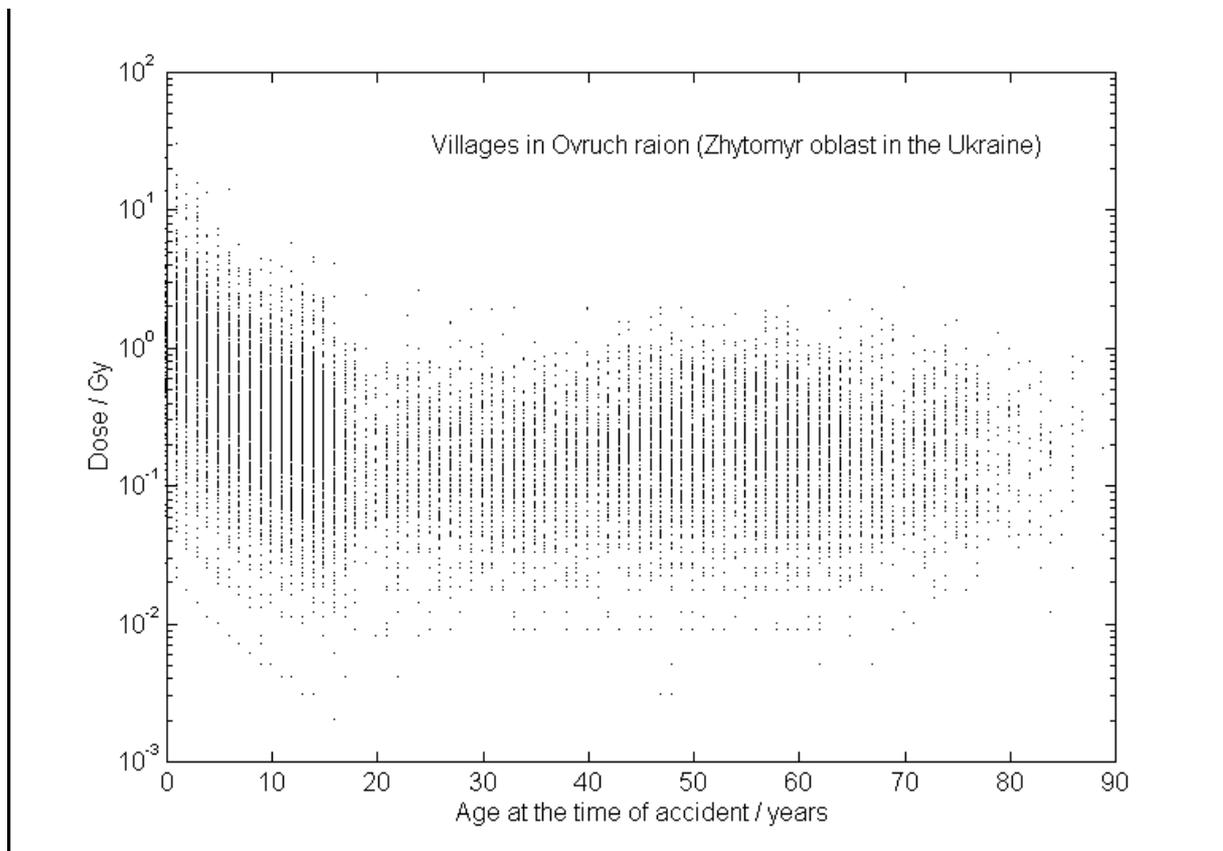
Figure 1. *Age-dependent individual doses in the rural settlements of Ovruch raion [7].*

At the first stage of the dose assessments (1986-1991) direct measurements of ^{131}I activity in the thyroids were analyzed and doses in the areas with such monitoring measurements were estimated (individual and average age-specific in the several raions and big towns) [20]. Figure 1 presents examples of these estimates for rural settlements of Ovruch raion (Zhytomyr oblast) [7]. Similar results were reported for Belarus and Russia [4,35]. These estimates show, on the one hand, pronounced age-dependence and, on the other hand, a large variability of the doses for the same age. Individual doses in the same age-group vary up to two orders of magnitude for the relatively large area like a raion. In small villages such variability is in the range of about 5-10. Age-dependent average doses in the settlements were assessed on the basis of individual doses [4,7,20,22,35].
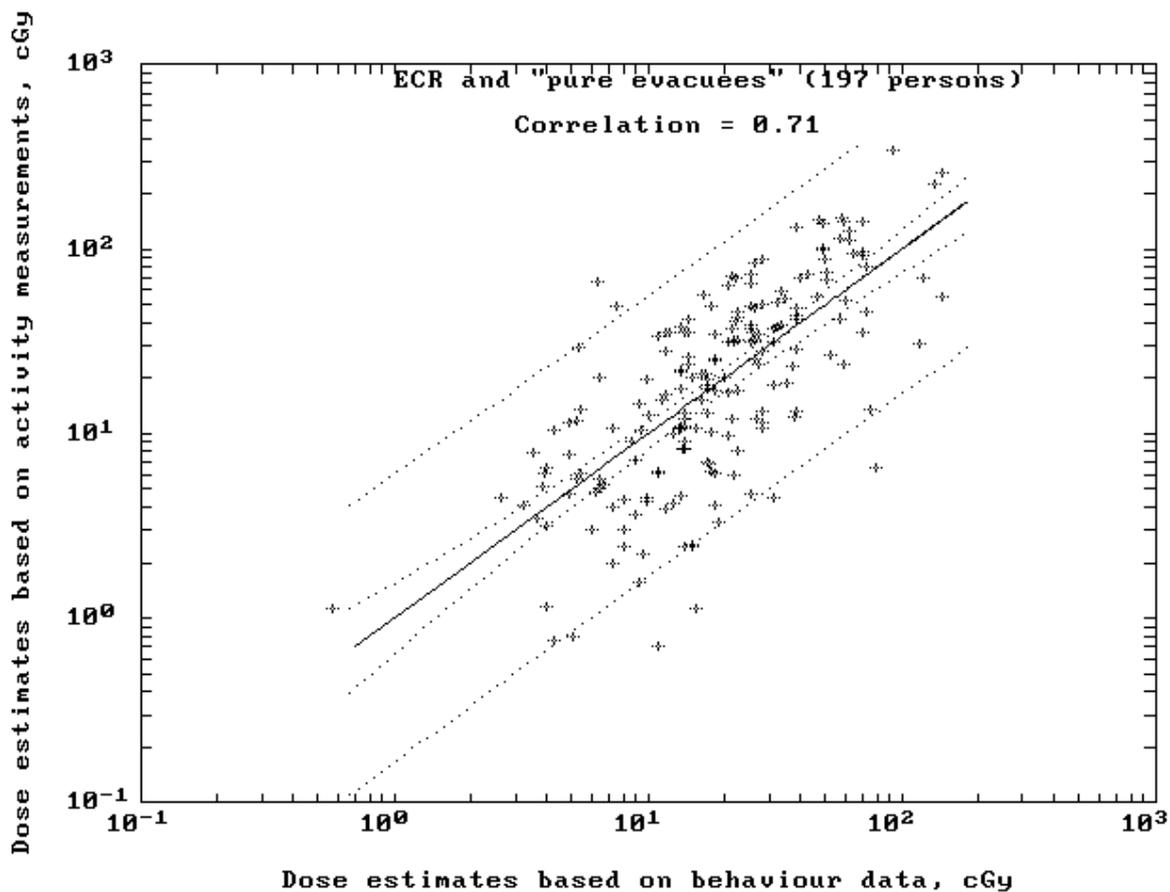
Figure 2. *Thyroid doses of the evacuees calculated on the basis of the results of measurements, and estimated on the basis of behaviour factors. The crosses refer the 197 evacuees with high quality measurements, the lines - to the 95 % confidence intervals for mean and individual values [6].*

Applying of data about individual behaviour is an alternative method for the assessment of individual doses. This method can be used only in combination with dose estimates based on ^{131}I activity measurements in the thyroids or on the results of radioecological models [3,6]. Figure 2 presents the comparison of the doses based on individual factors (age, cumulative gamma-dose in air at the place of residence, intake of stable iodine) and based on ^{131}I activity measurements in the thyroids for the evacuees from Pripyat town [6].

Doses for different populations

Individual doses are the basis for the estimation of average exposure in different population groups. In the Ukraine average age-dependent doses were assessed in each settlement where ^{131}I activity measurements were performed. Than these age-specific doses were interpolated and extrapolated to other closely located settlements based on correlation with ^{137}Cs deposition, distance and direction relative to the Chernobyl nuclear power plant [7,22,25]. Figure 3 presents the spatial pattern of the average thyroid doses in three northern Ukrainian oblasts [25]. This area includes settlements with and without monitoring measurements [7,20-22,25]. At present time a more advanced model is being developed for the assessment of individual and age-specific doses in different locations. This model is based on more realistic intake functions. To evaluate these functions the results of atmospheric dispersion modeling are used as well as additional information on

behaviour factors. Similar methods based on empirical relationships between individual doses and ^{137}Cs deposition were developed in Belarus and Russia [4,35].

[131]I environmental transfer model was applied to estimate thyroid doses for different population groups in Belarus [3]. This model is based on the ratio between ^{131}I and ^{137}Cs ground deposition estimated in the southern raions of Gomel and Mogilev oblasts. Available environmental data were analyzed and the important radioecological parameters were assessed, i.e. a) the elimination rate of ^{131}I from grass due to the weathering and growth dilution, b) the initial interception of ^{131}I by vegetation, c) the transfer coefficient for ^{131}I from grass to cow's milk, d) the yield of pasture grass, and e) the milk consumption rate. Additionally, the influence of applied countermeasures has been taken into account, such as the interruption of locally produced milk consumption, and appropriate correction factors have been estimated. The results are presented in Figure 4.
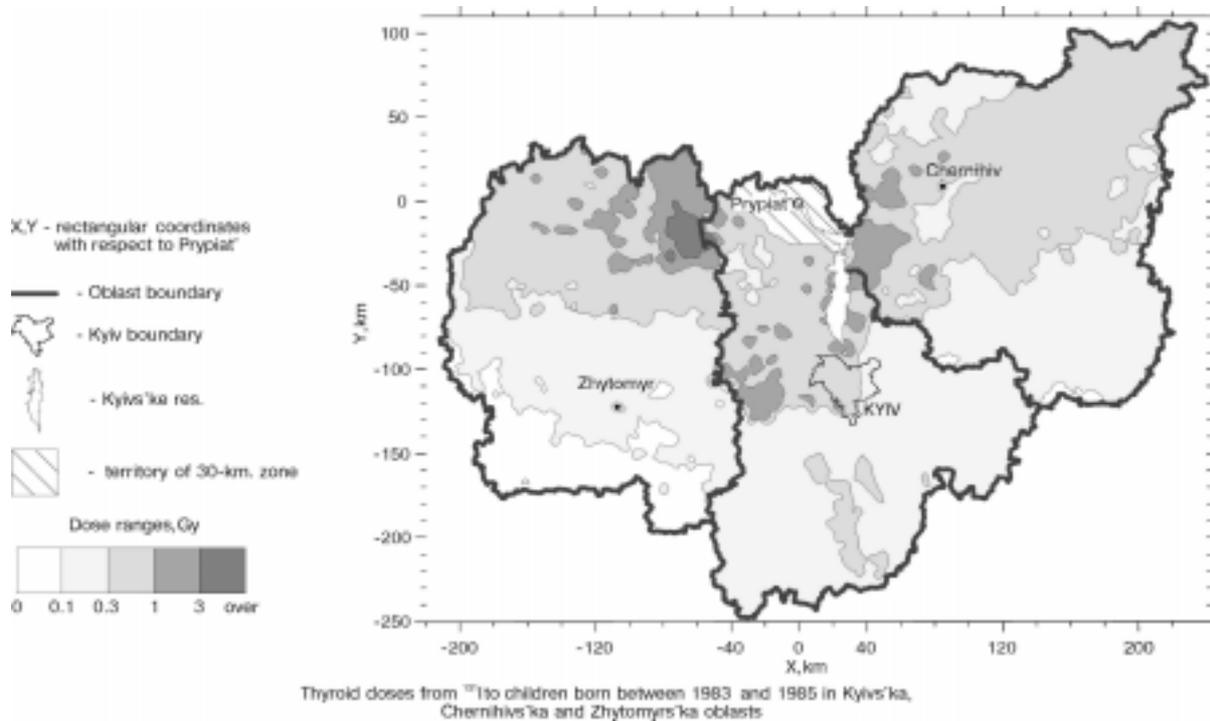

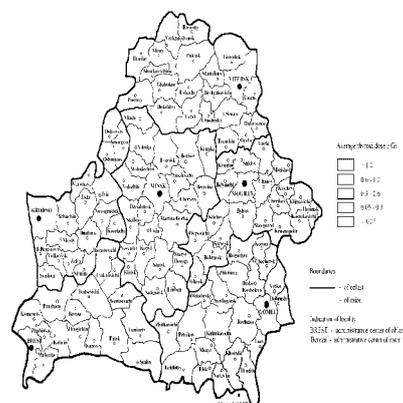*Figure 3. Geographical pattern of thyroid doses for children born in 1983-1985 in the northern Ukraine [25].*

Figure 4. Geographical pattern of thyroid doses for children in age of 0-14 y from

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Short-lived isotopes, ^{137}Cs and external exposure

For the early evacuees, up to 30%-40% of the thyroid exposure was assessed to be due to short-lived radioisotopes of iodine (^{132}I, ^{133}I, ^{135}I) [5]. This maximal value was obtained assuming inhalation during 1 hour at the time of 1 hour after the accident and a subsequent evacuation to a non-contaminated area. For people who were not evacuated for more than one week, the contribution of ^{132}I, ^{133}I and ^{135}I together did not exceed 5%-10%. More than 70% of the internal thyroid dose of the population in the contaminated area was due to ^{131}I [35]. Contribution of external exposures was negligible [26].

Uncertainties

Estimation of the dose uncertainties is very important for the epidemiological studies. Sensitivity analysis shows that natural variability of the thyroid mass is a main contributor to the final uncertainty of the dose estimated on the basis of ^{131}I activity measurements [8]. Contribution of thyroid mass to the variance of the dose is about 40-60 % depending from age and conditions of measurements. The second important source of uncertainties is error in the measurements of ^{131}I activity in the thyroid. For the good quality measurements this factor can contribute up to about 25-30 % to the variance of the dose [8,23]. If measurements were performed with non-spectrometric devices and without collimators this factor can become much more important due to variability of contribution of extra-thyroidal activity. Uncertainties due to variability of the thyroid mass or errors of the measurements can not be reduced. Influence of the third important source of uncertainties (15-25%) - unknown date and duration of fallout - can be reduced. Presented sensitivity analysis does not consider another possible contributor to the variance of the thyroid dose - uncertainties due to the modeling of the intake function. Much more additional efforts should be made to solve this problem. It should be mentioned that estimation of the uncertainties for the individual doses based on different correlation methods is even much more complicated.

2.   RISK ANALYSIS

Excess relative risk (ERR) and excess absolute risk (EAR) models are applied to described radiation-induced risk for the thyroid cancer.

According to the excess relative risk model disease rate observed in the exposed population is proportional to the background incidence:

$$r = r_0 (1 + \alpha_1 D + \alpha_2 D^2),$$

where r - disease rate, r_0 - background thyroid cancer rate, α_1 - parameter measures the unit increase in excess relative risk per Gy (ERR per Gy), α_2 - parameter described the deviation from the linear model.

According to the excess absolute risk model disease rate observed in the exposed population is a sum of background and radiation-induced incidence:

$$r = r_0 (1 + \beta_1 D + \beta_2 D^2),$$

where β_1 - excess absolute disease rate per Gy (EAR per Gy), β_2 - parameter described the deviation from the linear model.

2.1. External exposure

Estimations of the excess relative risk after the external exposure have been recently summarized by E. Ron et al. [31]. Results of this pooled analysis of five epidemiological studies can be summarized as following:

- thyroid is highly sensitive to the carcinogenic effects of radiation;
- linear dose-response model can be used to describe ERR and EAR in a wide range of the doses;
- pooled ERR is 7.7 Gy^{-1} (95% CI = 2.1, 28.7);
- pooled EAR is 4.4 per 10^4 PY Gy (95% CI = 1.6, 10.0);
- females have a higher risk than males;
- no excess risk was observed in the first five years after the exposure;
- there is a drastic increase of risk among people exposed in childhood (up to 15 y) starting 5-9 years after exposure, ERR is highest about 15 years after exposure, ands increase is observed during the entire follow up period (40 or more years after exposure);
- ERR is most apparent among persons irradiated before age 5.

In addition, it was found in this analysis that the ratio of the ERR for fractionated to single exposure is 0.7 (95% CI = 0.5, 1.1).

2.2. Internal exposure

Very few systematic epidemiological studies have been conducted to estimate the association between thyroid cancer and internal exposure due to radioiodine. The results of these investigations were analyzed by R. Shore [33]. It was found that ^{131}I is about 20-25% as effective as external irradiation in inducing thyroid cancer among juveniles. This conclusion should be taken with some caution because data on ^{131}I exposure to children are sparse. Table 3 presents the description of the most reliable studies excluding those considering high-dose ^{131}I therapy and adults exposure. All these studies had low statistical power due to small collective thyroid doses in the cohorts.

The ^{131}I dose to the Marshall Islands was only 10-20 % of the total dose, 80-90 % of the dose was due to short-lived radioiodines and external gamma-radiation.

Table 3. Estimates of thyroid cancer risk for juvenile from medical exposure to radioactive iodines and atomic weapons fallout (citation from [33]).

Study	Age at irradiation	No. irradiated persons	Mean year follow-up	Mean dose, Gy	Observed/expected cancers	ERR per Gy (90% Ci)	EAR per 10^4 PY Gy (90% Ci)
Swedish diagnostic ^{131}I [13]	0 - 19	≈2 000	20	1.6	2 / 1.2	0.5 (<0-2.6)	0.2 (<0-0.9)

FDA (US) diagnostic [131]I [11]	0 - 20	3 503	27	≈0.6	4 / 1.4	3.1 (<0-2.3)	0.5 (<0-3.5)
Utah ^{131}I fallout [28]	0 - 9	1 962	≈32	≈0.2	6 / 9	0.0 (0-3.7)	0.0 (0-5.6)
Marshall Islands [19,29]	0 - 18	127	32	12.4	6 / 1.2	0.3 (0.1-0.7)	1.1 (0.4-2.3)

The latest results of Swedish ^{131}I diagnostic study was recently published [10]. Hall et al. observed a small excess risk (about 2-10 times lower than that one predicted from data for the A-bomb survivors) among people under 20 years old when ^{131}I was administered. But only 300 of the 2408 people in the cohort under age of 20 were younger than 10 years (the most sensitive age). A small risk found in this study should be considered with caution.

The cohort study of the thyroid disease in relation to fallout from nuclear weapons testing in the USA should be also mentioned [17]. Eight thyroid cancer cases were registered in this investigation (study cohort 2 473 persons, average dose 98 mGy). Positive but non-significant dose-response was found for carcinomas.

2.3. Chernobyl experience

The accident in the Chernobyl nuclear power plant is a new source of information on the thyroid cancer risk after ^{131}I exposure. Large amounts of ^{131}I was released during the period from April, 26 to May, 6 1986. An increase of the thyroid cancer incidence in Belarus, Ukraine and Russia was reported regarding people exposed during childhood or adolescence [2,7,14,15]. Latency period for the radiation-induced thyroid cancer of three years observed after the accident is shorter than reported for the external exposure [12].

A case-control study with 107 thyroid cancer cases and two matched control groups of the same size indicated a strong relationship between thyroid cancer and radiation dose from the Chernobyl accident [1]. Two ongoing cohort studies with persons for whom the ^{131}I activity in the thyroid has been measured during the first two months after the accident would be expected to give reliable results about the thyroid cancer risk due to [131]I. But a long observation time is necessary to gather enough cancer cases.

Aggregate studies have many advantages and allow us to estimate radiation-induced risk for the thyroid cancer based on available data. On the one hand, hundreds of excess thyroid cancer cases have been already registered and average thyroid doses can be reconstructed with a higher reliability than individual thyroid doses. On the other hand, the appropriateness of aggregate studies to derive quantitative information on risk is limited to special cases [9,32]. A linear dose-response relationship and a control of confounding factors are essential for deriving reliable results.

Buglova et al [2] analyzed the thyroid cancer incidence in the period 1990-1992 among the children of eight most contaminated rayons in Belarus. Reported risk is very close to

the risk for the external exposure, but possible screening effects have not been taken into account.

The results of the aggregate study performed in the area including children of 0-15 years old at the time of the accident (birth cohort 1971-1986) from 5 821 settlements (towns and villages) in the Ukraine, Belarus and Russia have been recently published [15]. Average thyroid doses for this cohort were estimated in each settlement from the considered area. The variability of individual doses in the single settlements is smaller than the variability of the average doses. Figure 5 shows dose distribution in the birth cohort 1971-1985 [16]. The share of people in the whole cohort of population at lower thyroid doses is essentially larger than in the group with thyroid cancers. The dose distribution of the collective dose and cancer cases are very similar. Such similarity indicates the high correlation of thyroid dose and cancer cases. This observation is especially pronounced for the whole considered area. The population of Southern Ukraine (which was exposed to a negligible amount to the release from Chernobyl)
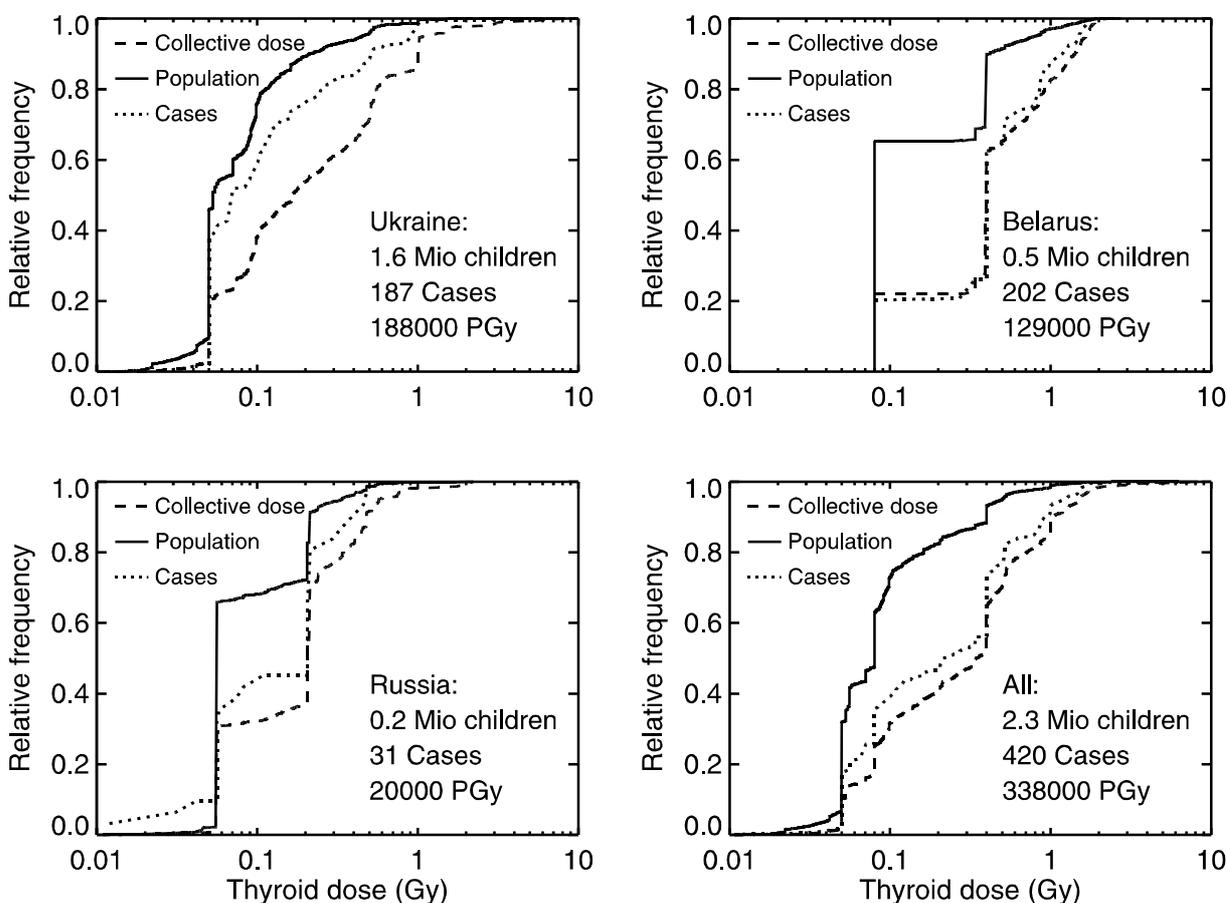

Figure 5. *Cumulative dose distributions of population, collective dose and thyroid cancer cases in the period 1991 to 1995 among the birth cohort 1971 to end of May 1986 in the study area [16].*

was chosen as a control group. Totally 420 thyroid cancers were observed in the cohort including 2 328 000 people. The excess thyroid cancer risk was shown to be a linear function of ^{131}I-dose in the range of 0.07-1.2 Gy (Figure 6). During the time interval of 1991-1995 an excess absolute thyroid cancer risk per unit thyroid dose of 2.3 (95% CI: 1.4-3.8) per 10^4 person-year Gy was observed. This excess absolute risk is comparable to the risk after external exposures. No significant differences both between countries and cities and rural areas were found. The ERR per unit dose ranges between 22 Gy^{-1} and 90

Gy^{-1} in different subareas. This values is larger than the best estimate of 7.7 (95% CI: 2.1; 28.7) obtained from
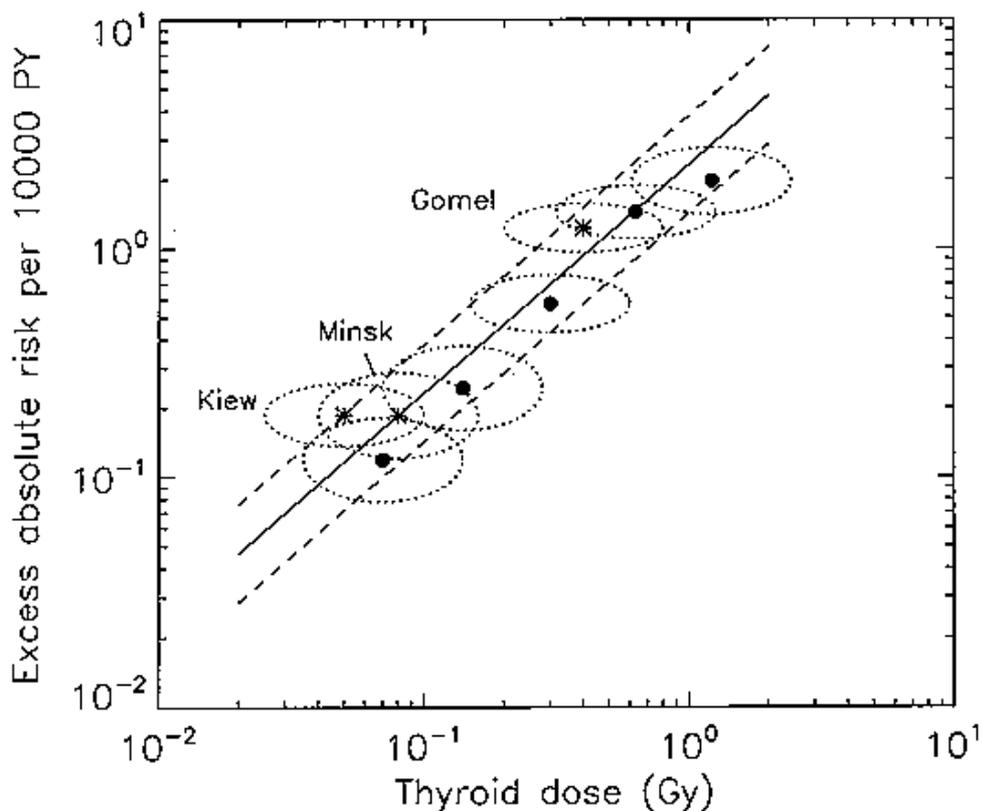

Figure 6*. Excess thyroid cancer risk in the period 1991-1995 among people born between 1971 and 1986. The dots indicate average values of settlements in the categories of dose 0.05-0.1, 0.1-0.2, 0.2-0.5, 0.5-1.0, 1-2 Gy; the stars show results for cities with large collective doses; PY = person-year. The solid line is the best estimate of the excess absolute risk per unit dose. Broken and doted lines indicate 95% confidence ranges [15].*

observations after external exposures [31]. The estimation of the relative risk is very sensitive to the variation of the background incidence. The monitoring effect can be much larger in the highly contaminated areas then in the Southern Ukraine. This can explain so high ERR observed in the study.

The analyzed data show some indication for a lower (about two times lower) efficiency per unit dose of ^{131}I as compared to external exposures (difference is not significant). Uncertainties of thyroid dose estimates have been identified as the main contributor to the variance of EAR per unit dose. The estimated ERR has a larger uncertainty than the EAR per unit dose, since the background incidence has a large uncertainty and contributes only a small portion to the observed cancer cases.

3. DISCUSSION AND CONCLUSIONS

Different methods were applied to reconstruct thyroid doses of different population groups in the Ukraine, Belarus and Russia. Models for the individual dose assessment based on ^{131}I activity measurements in the thyroids are generally similar. At present individual dose estimates are available for more than 300 000 people from the area up to 150 - 250 km from the Chernobyl nuclear power plant. Average age-specific doses were assessed for the people from the much larger territories based on radioecological and different extrapolation models (entire Belarus, northern Ukraine and Bryansk oblast in Russia). Average doses have smaller uncertainties, but their application in epidemiological studies is limited. Further efforts should be paid to improve models and estimate uncertainties of the doses.

The information on radiation risk for the thyroid gland is limited, especially for the internal exposure. Most of the existing studies have a small statistical power. The results reported after the Chernobyl accident can be very important for the assessment of the radiation-induced risk for the thyroid cancer after exposure to ^{131}I. The aggregate study using age-specific thyroid doses and thyroid cancer incidence among the selected populations can be used already now for the quantitative estimates of the risk. To compare the results from external and internal exposure cohorts of similar ages and gender structure should be used.

A recently published aggregate studies show the linear dose-effect response. The EAR per unit dose of 2.3 cases per 10^4 person-year·Gy (95% CI: 1.4-3.8) [15] estimated for the Chernobyl cohort can be compared with EAR of 4.4 cases per 10^4 person-year·Gy (95% CI = 1.6, 10.0) estimated on the basis of pooled analysis for the external exposure [31]. The EAR for the exposure due to ^{131}I is about two times smaller, but the differences are not significant. Taking into account that observation in the Chernobyl cohort is only 5-9 years after the exposure and the thyroid cancer incidence is still rising, we can conclude that there is no strong indication about higher effectiveness of the external irradiation.

The difference of the EAR for males and females in the Chernobyl study is consistent with observations after external exposures in the age before 15, where a difference by a factor of 2.5 was found. The ratio of the ERR for males and females exposed during childhood was found to be 2. It is consistent with the range of 0.2 to 2.6 observed in several studies for the external exposure [31].

New results recently obtained on the basis of Chernobyl data show in general good agreement with the previously published findings based on external exposure [31]. No significant difference between these two types of exposure was observed. This is the most important new information. Cohort of people exposed to ^{131}I after the Chernobyl is large. It includes all ages. Groups of people with very large collective doses can be selected for the different epidemiological investigations including cohort, case-control or aggregate studies. The improvement of the dose assessments, collection of the reliable and complete information about thyroid cancers and estimation of background incidence (assessment of the effect of thyroid surveillance) are the most important tasks for the future investigations. The radiation-induced risk for the thyroid cancer shows that this gland along with the breast and bone marrow is highly sensitive to radiation. Despite this the new results do not indicate any reasons to change waiting factor for this organ.

References

1) Astakova L.N., Anspaugh L.R., Beebe G.W., Bouville A., Drozdovitch V.V., Garber V., Gavrilin Y.I., Khrouch V.T., Kuvshinnikov A.V., Kuzmenkov Y.N., Minenko V.P., Moschik K.F., Nalivko A.S., Robbins J., Shemiakina E.V., Shinkarev S., Tochitskaya S.I., Waclawiw M.A. (1998) Chernobyl-related thyroid cancer in children of Belarus: A case-control study. *Rad Res* 150: 349-356

2) Buglova EE, Kenigsberg JE, Sergeeva NV Cancer risk estimation in Belarussian children due to thyroid irradiation as a consequence of the Chernobyl nuclear accident. *Health Phys* 71 (1996) 45-49.

3) Drozdovitch V.V., Goulko G.M., Minenko V.F., Paretzke H., Voigt. G., Kenigsberg Ya.I. Thyroid dose reconstruction for the population of Belarus after the Chernobyl accident. *Radiat Environ Biophys* 36 (1997) 17 - 23.

4) Gavrilin Y., Khrouch V., Shinkarev S., Drozdovitch V., Minenko V., Shemyakina E., Bouville A., Anspaugh L. Estimation of thyroid doses received by the population of Belarus as a result of the Chernobyl accident. In: *The Radiological consequences of the Chernobyl accident. Minsk, Belarus, 18-22 March 1996. EUR 16544 EN,* 1996, p. 1011-1020.

5) Goulko G.M., Kairo I.A., Sobolev B.G., Chepurnoy N.I. (1993) Methods of the thyroid dose calculations for the population of the Ukraine. In: *Actual questions of the prognose, current and retrospective dosimetry after the Chernobyl accident. Kiev, 27-29 October*, 1992. Kiev, 1993. 99-103.

6) Goulko G.M., Chumak V.V., Chepurny N.I., Henrichs K., Jacob P., Kairo I.A., Likhtarev I.A., Repin V.S., Sobolev B.G., Voigt g. Estimation of ^{131}I thyroid doses for the evacuees from Pripjat. *Radiat Environ Biophys* 35 (1996) 81-87.

7) Goulko G.M., Chepurny N.I., Jacob P., Kairo I.A., Likhtarev I.A., Pröhl G., Sobolev B.G. Thyroid doses and thyroid cancer incidence after the Chernobyl accident: assessments for the Zhytomyr region (Ukraine). *Radiat Environ Biophys* 36: 261-273 (1998).

8) Goulko G., P. Jacob, I. Likhtarev, I. Kayro, N. Chepurny, V. Shpak, A. Moskalyuk. Thyroid dose assessments after the Chernobyl accident: achievements and problems.

In: *International Symposium on Radiation and Thyroid cancer, Cambridge, UK, July 20-23*, 1998 (in press).

9) Greenland S and Robins J (1994) Invited commentary: Ecologic studies-biases, misconceptions, and counterexamples. *Am J Epidemiol* 139 747-760.

10) P.Hall, A.Mattsson, J.Boice. Thyroid cancer after diagnostic administration of iodine-131. *Radiation Research* 145, (1996), pp.86-92.

11) P.M.Hamilton, R.Chiacchierini, R.Kaczmarek. A follow-up of persons who had iodine-131 and other diagnostic procedures during childhood and adolescence. *Publ. FDA 89-8276, CDRH-Food & Drug Administration, Rockville, MD*, 1989, p.37.

12) Heidenreich W.F., Kenigsberg Y., Jacob P., Buglova E., Goulko G., Paretzke H.G., Demidchik E.P., Golovneva A. Time trends of thyroid cancer incidence in Belarus after the Chernobyl accident. Submitted to *Radiation Research*, 1998.

13) L.Holm, K.Wiklund, G.Lundell, N.Bergman, G.Bjelkengren,E.Cederquist, U.Ericsson, L.Larsson, M.Lidberg, R.Lindberg et al. Thyroid cancer after diagnostic doses of iodine-131: A retrospective cohort study. *J.Natl.CancerInst.* (1988), 80, p.1132-1138

14) Ivannov VK, Tsyb AF, Gorsky AI et al. Leukemia and thyroid cancer in emergency workers of the Chernobyl accident; estimation of radiation risks (1986-1995)*. Radiat Environ Biophys* 36 (1997) 9-16.

15) Jacob P, Goulko G, Heidenreich WF, Likhtarev I, Kairo I, Tronko ND, Bogdanova TI, Kenigsberg J, Buglova E, Drozdovitch V, Golovneva A, Demidchik EP, Balonov M, Zvonova I, Beral V Thyroid cancer risk to children calculated. *Nature* 392 (1998) 31-32.

16) P. Jacob, G. Goulko, W.F. Heidenreich, I. Kairo, I. Likhtarev, J. Kenigsberg, E. Buglova, I. Zvonova, M. Balonov, T.I. Bogdanova, N.D. Tronko, E.P. Demidchik. Thyroid exposures of children and adolescents due to the Chernobyl accident: the resulting cancer risk. In: *International Symposium on Radiation and Thyroid cancer, Cambridge, UK, July 20-23*, 1998 (in press).

17) Kerber RA, Till JE, Simon SL, Lyon JL, Thomas DC, Preston-Martin S, Rallison ML, Lloyd RD Stevens W (1993) A cohort study of thyroid disease in relation to fallout from nuclear weapons testing. *JAMA 270*: 2076-2082

18) E.T.Lessard, A.Brill, W.Adams. Thyroid cancer in the Marshallese: Relative risk of short-lived internal emitters and external radiation exposure. In: *Fourth International Radiopharmaceutical Dosimetry Symposium, CONF-851113, National Technical Information Service, Springfield, VA*, 1985, pp.628-647.

19) Likhtarev I.A., Shandala N.K., Goulko G.M., Kairo I.A. Conception of the permissible levels and the possibility of their realisation. *Hygiene and sanitary*. 1991, N 3, p. 86-88.

20) Likhtarev I.A. Shandala N.K. Goulko G.M. Kairo I.A. Exposure doses to thyroid of the Ukrainian population after the Chernobyl accident. *Health Phys* 64 (1993) p.594-599.

21) Likhtarev I.A., Goulko G.M., Kairo I.A., Los I.P., Henrichs K., Paretzke H.G. Thyroid exposures resulting from the Chernobyl accident in the Ukraine. Part 1: Dose estimates for the population of Kiev. *Health Phys* 66 (1994) p.137-146.

22) Likhtarev I.A., Goulko G.M., Sobolev B.G., Kairo I.A., Chepurnoy N.I., Pröhl G., K. Henrichs. Thyroid dose assessment for the Chernigov region (Ukraine): estimation based on ^{131}I thyroid measurements and extrapolation of the results to districts without monitoring. *Radiation and Environmental Biophysics* 33 (1994) p.149-166.

23) Likhtarev I.A., Chumak V.V., Repin V.S. Retrospective reconstruction of individual and collective external γ-doses of population evacuated after the Chernobyl accident. *Health Phys* 66 (1994) 643-652.

24) Likhtarev I.A., Goulko G.M., Sobolev B.G., Kairo I.A., Pröhl G., Roth P., Henrichs K. Evaluation of the ^{131}I thyroid-monitoring measurements performed in Ukraine during May and June of 1986 69 (1995) *Health Phys* p.6-15.

25) I. Likhtarev, B. Sobolev, I. Kairo, L. Tabachny, P.Jacob, G.Pröhl, G. Goulko. Results of large scale thyroid dose reconstruction in Ukraine. In *Proceedings of the first international conference Minsk, Belarus, 18 to 22 March 1996. EUR 16544 EN*, 1996, p. 1021-1034 (in English).

26) Minenko VF, Drozdovitch VV, Tretyakevitch SS, Ulanovsky AV (1996) Exposure of Belorussian population following the Chernobyl accident: Collective doses and prognosis of stochastic effects. *Medical and biological aspects of the Chernobyl accident* N4: 50-65.

27) Pitkevich V.A., Shershakov V.M., Duba V.V., Chekin S.Y., Ivanov V.K., Vakulovski S.M., Mahonko K.P., Volokitin A.A., Tsaturov Y.S., Tsyb A.F. Reconstruction of radionuclide composition of the deposition in Russia due to the Chernobyl accident. In *Radiation and Risk 3* (1993), p.62-93.

28) M.L.Rallison, T.Lotz, M.Bishop, W.Divine, K.Haywood, J.Lyon, W.Stevens. Cohort study of thyroid disease near the Nevada test site: A preliminary report. *Health Physics*, 59, 1990, pp.739-746.

29) J.Robbins, W.Adams. Radiation effects in the Marshall Islands. In: *Radiation and the Thyroid (S.Nagataki ed.). Excerpta Medica, Amsterdam*, 1989, p.11-24.

30) Romanenko A.E., Likhtarev I.A., Shandala N.K., Goulko G.M., Kairo I.A., Chepurnoy N.I. Hygienic analysis of the thyroid exposure of the Ukrainian population. *News of the Academy of medical science of the USSR*. 1991, N 8, p. 44-47

31) Ron E, Lubin JH, Shore RE, Mabuchi K, Modan B, Pottern LM, Schneider AB, Tucker MA, Boice JD (1995) Thyroid cancer after exposures to external radiation: A pooled analysis of seven studies. *Radiat Res* 141: 259-277

32) Sheppard L, Prentice RL, Rossing MA (1996) Design considerations for estimation of exposure effects on disease risk, using aggregate data studies. *Stat Med 15*: 1849-1858

33) Shore R.E. Issues and epidemiological evidence regarding radiation-induced thyroid cancer. *Radiation Research1* (1992), 131, p.98-111.

34) Tsyb A.F., Stepanenko V.F., Gavrilin Y.I., Khrouch V.T., Shinkarev S.M., Omelchenko V.N., Ismailov F.G., Peshakov C.Y., Yakubovich N.D., Proshin A.D., Kuzmin P.S. The problems of the retrospective estimation of exposure doses of inhabitants affected by the Chernobyl accident: peculiarities of forming, structure and level of irradiation according to the data of direct measurements. Part 1: Internal thyroid doses. *WHO/EOS/94.14, Geneva (1994).*

35) Zvonova I.A., Balonov M.I. Radioiodine dosimetry and prediction of consequences of thyroid exposure of the Russian population following the Chernobyl accident. *The Chernobyl paper. Vol. 1. Doses to the Soviet population and the early health effects studies, ed. by Mervin S.E., Balonov M.I. Research Enterprises, Richland, Wa.*, (1993) pp. 71-125.

FIGURES

Figure 1. Age-dependent individual doses in the rural settlements of Ovruch raion [7].

Figure 2. Thyroid doses of the evacuees calculated on the basis of the results of measurements, and estimated on the basis of behaviour factors. The crosses refer the 197 evacuees with high quality measurements, the lines - to the 95 % confidence intervals for mean and individual values [6].   **OK**

Figure 3. Geographical pattern of thyroid doses for children born in 1983-1985 in the northern Ukraine [25].   **OK**

Figure 4. Geographical pattern of thyroid doses for children in age of 0-14 y from Belarus [3].

Figure 5. Cumulative dose distributions of population, collective dose and thyroid cancer cases in the period 1991 to 1995 among the birth cohort 1971 to end of May 1986 in the study area [16]. **OK**

Figure 6. Excess thyroid cancer risk in the period 1991-1995 among people born between 1971 and 1986. The dots indicate average values of settlements in the categories of dose 0.05-0.1, 0.1-0.2, 0.2-0.5, 0.5-1.0, 1-2 Gy; the stars show results for cities with large collective doses; PY = person-year. The solid line is the best estimate of the excess absolute risk per unit dose. Broken and doted lines indicate 95% confidence ranges [15].

THYROID CANCER - AGE AND MOLECULAR BIOLOGY

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INTRODUCTION

Since the accident at Chernobyl nuclear power plant in April 1986 well over 500 cases of thyroid carcinomas have been reported in children in Belarus. Nearly all of them have occurred since 1990, before the accident only 1 or 2 cases a year occurred in Belarus. The numbers that would be expected to occur during 8 years since 1990 would be about 8, based on recorded Belarus incidence in the 10 years before Chernobyl, about 9 based on the UK incidence over a 30 year period, about 19 based on average international rates and about 56 based on some of the highest recorded international rates. The work to be presented will consider the verification of the pathological diagnosis of the cases, the type of tumour present, the molecular biological findings in these cases and the relationship between age at exposure and tumour incidence. Increases in childhood thyroid cancer have also been reported in the northern Ukraine and in the parts of the Russian Federation that are close to the Belarussian/Ukrainian borders. Evidence from these countries will also be considered, but the major analysis will be of the Belarussian cases, partly because Belarus was the country most heavily affected by fallout, and partly because all the cases of childhood thyroid cancer are by law operated on in one centre in Minsk, the capital of this country of just over 10 million people.

1. VERIFICATION OF THE PATHOLOGICAL DIAGNOSIS OF CHILDHOOD THYROID CANCER

This part of the work has been carried out in collaboration with the pathologists in 3 centres, Professor Cherstvoy and his staff in the Pathology Department of the University of Minsk, Belarus, Professor Lushnikov and his staff in the Pathology Department of RAMS, Obninsk in the Russian Federation and Dr Bogdanova and her staff in the Pathology Department, Institute of Endocrinology and Metabolism, in Kiev, Ukraine.

The arrangements in Minsk are complicated by the fact that a provisional diagnosis is made in a small pathology department in the Cancer Institute and the material is then passed to the University Department for the final diagnosis. We have studied 295 of the 539 cases diagnosed as childhood thyroid cancer in the University Department during the period January 1990 to December 1997, together with a further 131 other childhood or adolescent lesions and have confirmed the diagnosis of malignancy in 98% although in some cases the type of malignancy was changed on review.

In the Russian Federation an increased incidence of childhood thyroid cancer has been reported for the oblasts of Bryansk, Kaluga, Tula and Orel. The diagnosis here is established in the hospitals in which the children are operated, usually the main town in each oblast, some of the cases are sent to Obninsk for confirmation of diagnosis, but the collection in Obninsk is far from complete. The equipment available in the peripheral hospitals is often far from ideal. A small number of cases has been brought to Cambridge for review, but 52 cases from Bryansk were the subject of a formal review in Obninsk, in

collaboration with Professor Lushnikov of Obninsk and Professor Frank of the Cancer Institute in Moscow. Agreement between the 3 reviewers was very good, but agreement between the joint diagnoses of the reviewers and the original diagnoses from Bryansk was poor, with only 24 of the 52 cases confirmed as cancer. In some cases this may have been due to the extent and quality of the material available for review, but in a significant number of cases it was considered that there was a straightforward diagnostic error. The commonest reason for this was making a diagnosis of papillary cancer in a follicular adenoma on the basis of some areas of papillary infolding in an encapsulated tumour with none of the cytological features of papillary carcinoma and no evidence of any invasion.

In the Ukraine, the Institute of Endocrinology and Metabolism in Kiev provides the care for children with thyroid abnormalities from the northern part of the Ukraine, including the 6 contaminated oblasts that included Chernobyl and the adjacent areas that also border the contaminated areas of Belarus. The diagnosis of thyroid cancer is made in the pathology department of the institute 202 cases of childhood thyroid carcinoma and 59 other cases have been reviewed and 98% agreement reached on the basis of malignancy. As in Belarus some of the cases originally diagnosed as malignant but regarded as benign on review showed the morphological features of dyshormonogenesis. In both Belarus and the Ukraine cases from the early part of the increase and recent cases have been reviewed and the high level of agreement has been maintained.

2.   HISTOLOGICAL TYPE OF CANCER

The striking findings on reviewing the histology of the cases was the enormous predominance of papillary carcinoma. In the series from England and Wales, papillary carcinoma formed about two thirds of all thyroid cancers under the age of 15, in Belarus this figure was 97.5% and in the Ukraine 91%. In the Russian Federation the proportion drops to 78%, intermediate between the over 90% found in Belarus and the Ukraine and that found in England and Wales. Follicular and medullary carcinomas were relatively uncommon with a total of 11 follicular and 2 medullary carcinomas in children over an 8-year period in Belarus, using England and Wales figures about 2 of each type might have been expected.

Papillary carcinomas can show a range of histological appearances, but the cases occurring in the exposed population were commonly of a solid type of tumour, recognisable as belonging to the papillary group because of the occurrence of a minor papillary component, of psammoma bodies, of the nuclear features (although less marked) and of the unencapsulated locally invasive growth and lymph node metastasis typical of papillary rather than follicular carcinomas. All of the large number of cases diagnosed as papillary carcinomas tested showed positivity for thyroglobulin by both immunocytochemistry and insitu hybridization and were negative for calcitonin by both techniques. A proportion of the tumours did show included C Cells, a finding relevant to some of the molecular biological investigations but otherwise simply indicative of invasive tumour growth. In the England and Wales series the classical type of papillary carcinoma was the commonest, but the solid and follicular tumours were most frequent in the children under the age of 10; with the approach of puberty the classical type became dominant. The sex ratio also changed being close to equality in young children with females becoming preponderant in the older children. The evolution of changes with time in the tumours from children exposed to fallout from Chernobyl have been followed. The solid type of tumour was much the most common in the earliest cases, as time passed these tumours showed a greater proportion of a follicular component. The proportion of

the classical papillary carcinomas has not increased with the increasing age of the children as it did in the UK study, suggesting that the solid/follicular type of papillary carcinoma might be specifically linked to the exposure. The proportion of all papillary carcinomas which are of the solid follicular subtype is 76% in the Belarussian children, 69% in children from the Ukraine and 57% in the reviewed cases from the Russian Federation, again an intermediate figure between that found in the heavily exposed children of Belarus and Ukraine and that found in England and Wales (33%).

The early tumours in Belarus were large, many were locally invasive. With time the size of tumours resected and the clinical stage has reduced, suggesting that tumours are being recognised at an earlier stage in their development. However very few tumours have been classified as microcarcinomas. The situation is complicated by the definition of microcarcinoma in adults, where a size of 1 cm in diameter is used. The evidence that these smaller tumours are unaggressive is entirely derived from adult studies. In the children in Belarus and the Ukraine, primary tumours of less than 1 cm diameter are commonly associated with extensive local invasion both within and outside the gland, so that in the study reported here the diagnosis of microcarcinoma has been applied only to tumours of no more than a few millimetres in diameter, lacking evidence of widespread invasion.

3.   MOLECULAR BIOLOGICAL STUDIES

Studies of the genes involved in the development of tumours have been carried out by a number of groups. Some of the early studies involved a small number of tumours, but did find rearrangement of the ret oncogene, particularly ret PTC 3 rearrangement. Our own group in collaboration with centres in Brussels, Munich and Naples have studied 152 cases. We found that 56 of these showed ret rearrangement, all were papillary carcinomas. Of these cases 25 were ret PTC I and 29 ret PTC III, one case showed both rearrangements.   We found no ras mutations in any of the 52 cases tested, and no mutations in the exons studied in the p53 gene or in the TSH receptor gene. These findings are in keeping with those expected in papillary carcinoma, p53 is linked to the differentiated to undifferentiated carcinoma transition and ras mutations occur in follicular rather than papillary carcinoma. It is not possible at present to say if the ret PTC III rearrangements are more common in radiation induced than non-radiation induced tumours, particularly as adequate studies of the frequency of the different types of ret rearrangement in sporadic papillary carcinomas in children have not yet been reported. It is possible to say that there is not a single molecular biological change which distinguishes these post-Chernobyl tumours from sporadic apparently non-radiation induced tumours. There is a strong correlation between the molecular biological findings and the morphological changes, with ret PTC III largely confined to tumours with the solid follicular pattern, (26 of 29 PTC III positive tumours were of this subtype) and ret PTC I mainly found in tumours of the classical or diffuse sclerosing subtypes (16 of 25 PTC I positive tumours were of these subtypes).   This confirms that they may have differing clinical characteristics and possibly also differing incidences with time after exposure.

## 4.   GEOGRAPHICAL DISTRIBUTION OF THE CASES

The epidemiology will be dealt with separately, but the oblast of residence of almost all the histologically confirmed cases was available. Almost exactly 50% of the Belarussian

cases came from the Gomel oblast, the most heavily exposed area, which borders the oblasts with the highest incidence in the Ukraine. The oblast with the lowest incidence was Vitebsk, here the incidence was considerably higher than that seen in Belarus post Chernobyl, and was almost 6 times that seen in England and Wales. This level of increase might well be due to increased ascertainment, but in the other oblasts, hundreds of kilometres from Chernobyl the incidence varied from about 10 per million per year to 44 per million per year in Brest and 83 per million per year in Gomel (Figures 1 and 2).

Figure 1

Childhood thyroid cancer in children in Belarus, 1990 - 1997 inclusive

Crude incidence figures (per million per year)
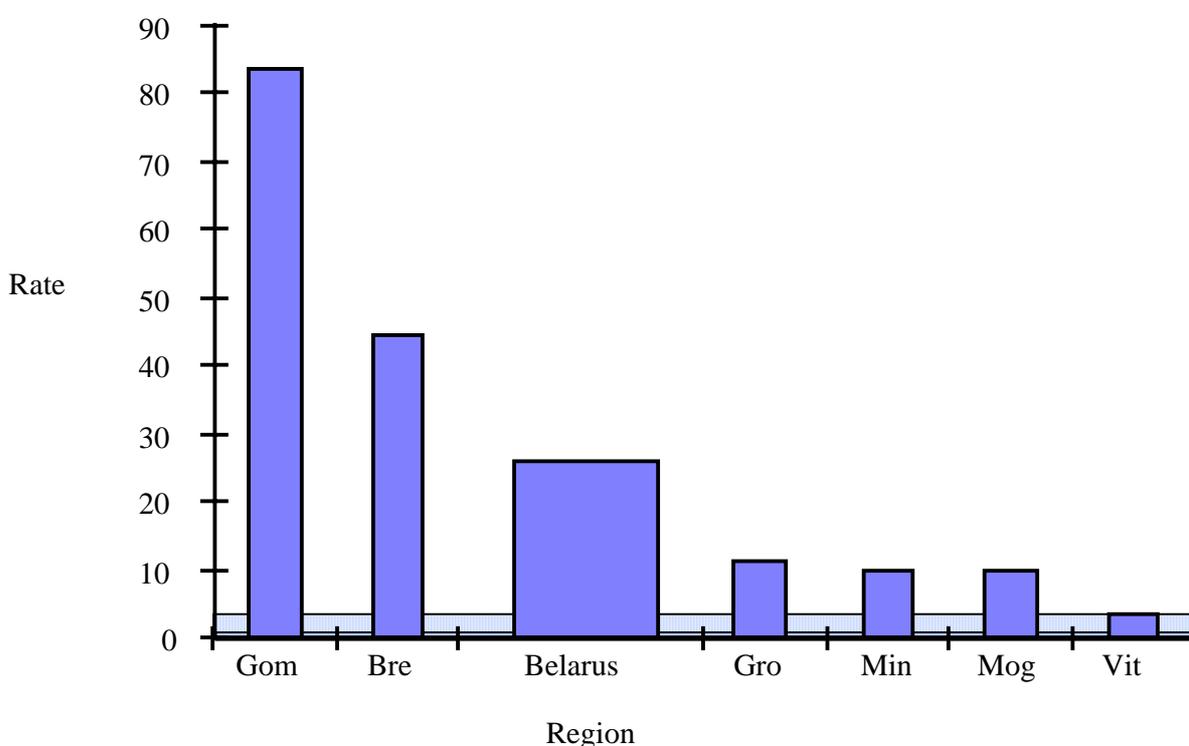
The upper horizontal line represents the upper limit of expected normal incidence the lower horizontal line represents the UK incidence rates.

These figures are derived from exposed cohorts during 1990 - 1997 inclusive.   8 cases have been confirmed in children born in 1987 or later, a rate slightly lower than that seen in Vitebsk for exposed children and just above the upper end of the range that can be regarded as normal.

<u>**Figure 2**</u>

Incidence rate of childhood thyroid cancer in the oblasts of Belarus during 1990 - 1997.

The shaded areas represent the heaviest areas of Cesium fallout.
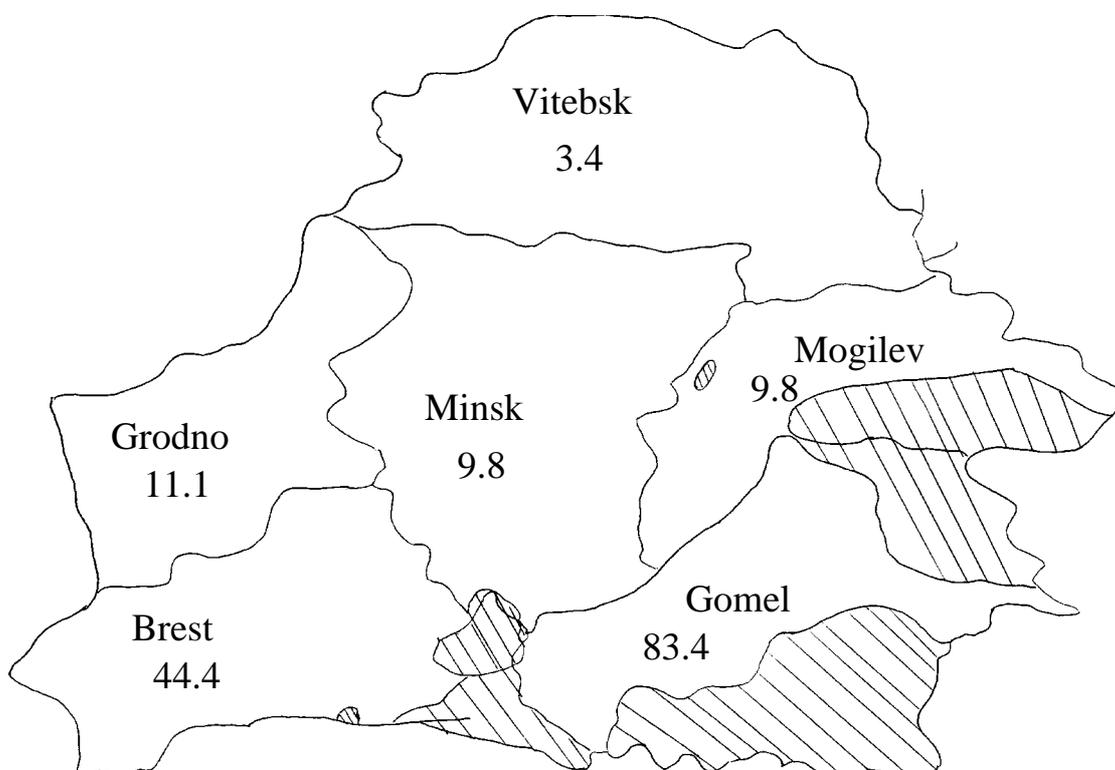

5.   EXPOSURE TO FALLOUT AND THYROID CANCER

The large rise in the incidence of confirmed cases of thyroid carcinoma in children exposed to fallout from the Chernobyl nuclear accident, the correlation of incidence and extent of fallout and the rapid drop in incidence to near normal figures in children born more than a few months after the accident combine to show a causal connection between exposure and carcinogenesis. The fact that isotopes of iodine were the largest component of the released radioactivity, apart from the inert gas Xenon, the known ability of radiation to cause thyroid cancer, the 1000 to 2000 fold greater radiation dose to the thyroid from radioactive isotopes of iodine compared to the rest of the body, together with the lack of any confirmed report of increased carcinogenesis in any organs other than the thyroid combine to suggest very strongly a causal connection between exposure to radioactive isotopes of iodine and the development of childhood thyroid cancer. The dose response relationship is not the subject of this paper. However there remains the question as to why the increase has been so marked in children. An increase has been reported in adults, this increase of almost 2 to 3 fold, has not been subject to the same verification, and is of the same order as the apparent change in the least exposed oblast and the apparent increase between the recorded pre-Chernobyl incidence in Belarus as a whole and the incidence in the children born after the Chernobyl accident. To explore this increased sensitivity of children as compared to adults further, the relationship between age at exposure and incidence of thyroid cancer in children has been studied.

6.   AGE AT EXPOSURE AND INCIDENCE OF CHILDHOOD THYROID CANCER

The normal relationship between age and incidence of childhood thyroid cancer, as shown by the study of over 150 cases occurring over a 30 year period in England and Wales is one of accelerating increase with age, from a rate of about 0.05 per million per year for children aged 4 - 5 years to 1.4 per million per year for children aged 14. After adolescence the rate of increase slows during the reproductive years, accelerating again after the menopause. Apart from the early years there is considerably higher incidence in females than males. The observed incidence for the cases in Belarus was calculated for cohorts of 1 year, from those under 1 at exposure to those aged 8 at exposure and were compared with the incidence expected from the England and Wales data. The figures show a smooth drop in the sensitivity to the thyroid carcinogenic effect of exposure to fallout in those under 1 at exposure, falling to about a 20 fold increase at age 8.

Figure 3

Comparison of Observed: Expected incidence of childhood thyroid carcinoma in cohorts of 1 year by age at exposure (children in Belarus between 1990 - 1997 inclusive, compared to children in the UK 1963 - 1992)
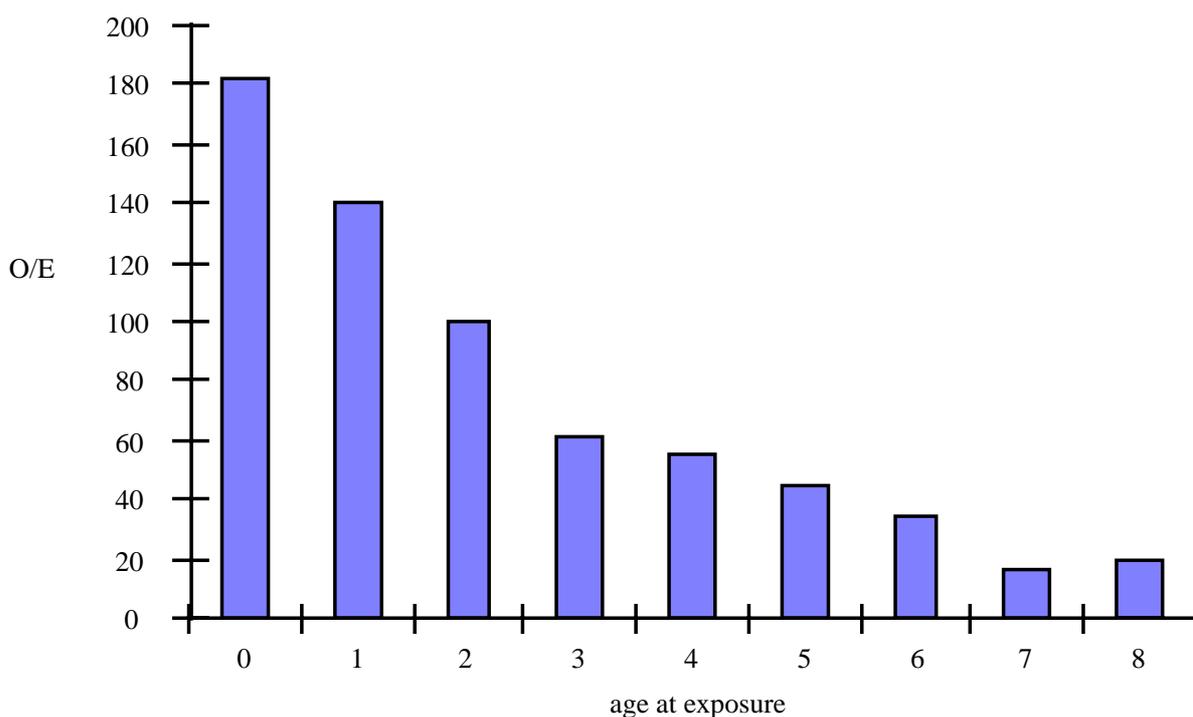
This observation has been further analysed in two ways, by comparing the rate of increase in numbers of cases with age at exposure and by analysing the numbers and observed/expected ratio for each exposed cohort with age at operation. The rate of increase in numbers of cases using 2 year cohorts was greatest in the 0 - 1 cohort and least in the 6 - 7 cohort, in each cohort the observation was consistent with a straight line increase (figure 4); while the natural increase is sigmoidal. Analysis of the numbers of cases for each cohort and year of age at operation shows that in the two youngest exposure cohorts the rate of increase may have diminished or even reversed, possibly with a peak at age 8 in those under 1 at exposure and at age 11 in those aged 1 at exposure.

Figure 4

Number of cases of childhood thyroid carcinoma in Belarus related to age at operation; 2 year cohorts by age at exposure
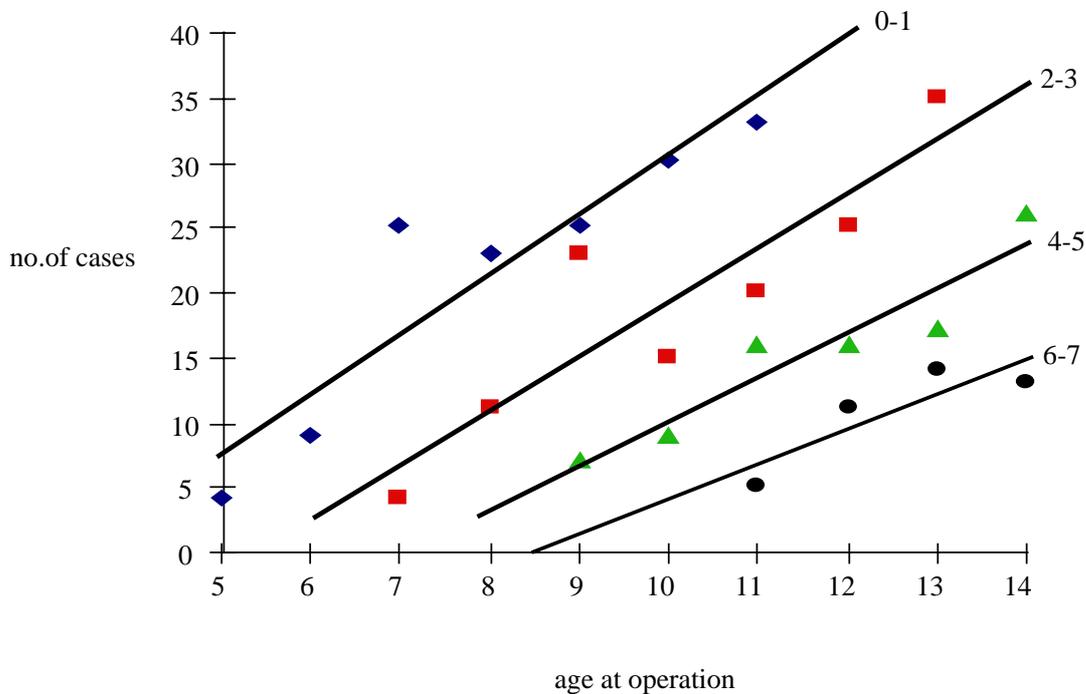
The number of cases for each point is not sufficient to say more than there is a decrease in numbers in the recent periods, while an increase would have been predicted at these points if the increase was following the incidence changes with age seen in an unexposed population. This is more clearly shown when the observed: expected ratio is calculated for the exposed cohorts aged under 1 for each year of age at operation (figure 5). These observations raise the possibility that the youngest children at exposure show the most rapid rate of increase but reach an earlier peak of incidence. Whether they will show a more rapid decline or whether the incidence will plateau remains to be revealed. This situation has some similarities to the incidence of childhood leukaemia after exposure to external radiation.

Figure 5

Changes in Observed: Expected ratio of thyroid carcinoma incidence for each year of age at operation for children aged under 1 at the time of the Chernobyl accident

age at operation (Cohort 0 at exposure)
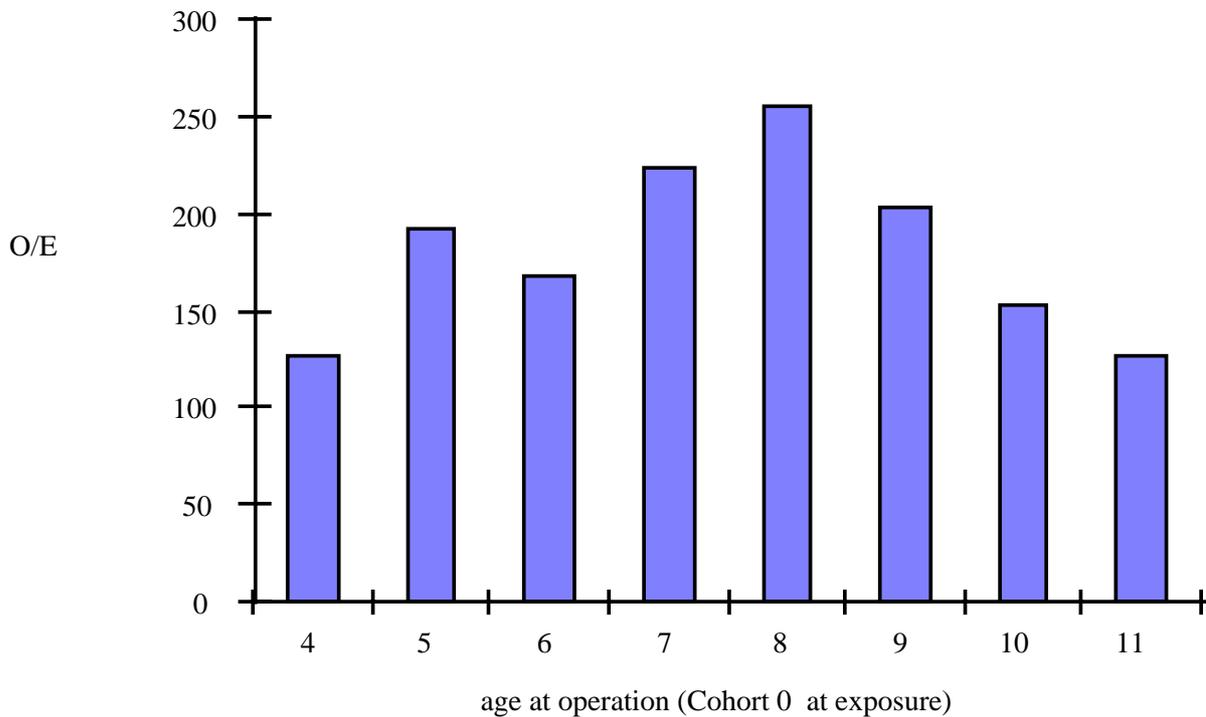
7. FUTURE DEVELOPMENT

It can be seen that it remains difficult to predict the future development of the incidence of thyroid cancer in the exposed population. The apparent downturn, although supported by observations in adolescents remains to be substantiated. The identification of two subtypes of papillary carcinoma characterised by differing morphology and differing molecular biology raises the possibility that they may follow different time courses for incidence. While the observations have been broken down in this way, the figures for the classical/and diffuse sclerosing types become too small to be reliable. It also remains possible that follicular carcinomas have a much longer latent period than papillary carcinoma, so that an increase in follicular carcinoma may yet occur. In support of this is the observation by a Japanese study of a high frequency of thyroid nodules in children in Gomel, compared to other regions around Chernobyl, even though other regions had a much higher incidence of goitre. This is supported by a pilot study, which shows that among children with thyroid adenomas operated on in Minsk the proportion that come from Gomel is increasing with time and approaching the 50% seen with papillary carcinoma. Follicular carcinomas are considered to arise from adenomas, so that there is a significant possibility that an increase of the incidence of follicular carcinomas may occur in the future. There remains also the possibility of an increase in non thyroid tumours, perhaps particularly those arising in the tissues that also shows a concentration of radioiodine, although to a very much lower level than the thyroid.

8. CONCLUSIONS AND SUMMARY

This study of the thyroid carcinomas which have been reported to occur in a large number of children exposed to high levels of fallout from Chernobyl has shown

(i)   The diagnosis of malignancy in thyroid specimens made in the Department of Pathology in the University of Minsk and in the Institute of Endocrinology and Metabolism in Kiev show a high level of accuracy as judged by international standards.

(ii)   The tumours are not trivial carcinomas, they show a high frequency of wide invasion within the thyroid and of invasion of extrathyroid tissues. Very few are truly occult microcarcinomas. Over 500 carcinomas have occurred in children in Belarus during the years 1990 - 1997.

(iii)   The tumours are almost exclusively papillary carcinomas.

(iv)   A high proportion of the papillary carcinomas are of a solid follicular subtype which is uncommon in adults.

(v)   The main molecular biological changes so far identified in these tumours are in the ret oncogene. Ret PTC III rearrangement was predominant in early cases, this may be radiation related or may be age related. No firm evidence of a radiation signature has yet emerged.

(vi)   Almost 50% of the cases in Belarus have occurred in the Gomel oblast which has less than 20% of the population of Belarus and was the most heavily exposed. Other oblasts also show an increased incidence particularly Brest, the increase in Vitebsk, the most northerly and least exposed oblast was within the range expected for increased ascertainment.

(vii)   The distribution of these cases broadly conforms to the areas of highest exposure; the incidence dropped dramatically in children born after Chernobyl.

(viii)   The present figures show a marked age related change in sensitivity to the carcinogenic effect on the thyroid of exposure to fallout, with children aged under 1 at exposure showing an approximately 10 fold increase over children aged 8. However there are recent indications that this great increase linked to an early age at exposure may be accompanied by an earlier peak in incidence, so caution must be exercised before assuming that the existing ratio will be continued in adult life.

(ix)   It can be concluded that there is no doubt that exposure to fallout from the Chernobyl nuclear accident has led to a large increase in the incidence of thyroid carcinoma in exposed children and that this increase is attributable to radioiodine in fallout. The increase has been detected hundreds of kilometres from the reactor at Chernobyl. The youngest children at exposure have shown the highest relative increase in the incidence of thyroid cancer, this is consistent with studies of children exposed to X-rays and the lack of sensitivity of adults to radiation carcinogenesis in the thyroid. Because of the possibility that a more rapid initial increase in the younger children may be accompanied by an earlier peak in incidence, it is too early to say what the age related life time risk will be.

PREVENTION AND DIAGNOSIS OF RADIATION INDUCED THYROID DISEASES.

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One of the major health consequences related to the Chernobyl disaster is the sudden and great increase in the number of people with thyroid carcinoma, particularly children. In the twelve years following the disaster a total of 5449 cases of thyroid cancer have been diagnosed in the Republic of Belarus, corresponding to a 3.9 fold increase with respect to the 12 years before the accident. This increase is age-related, resulting in a 75 fold increase in children, 10.1 in adolescents, 3.7 in young adults, and 3.4 in adults. A great increase of thyroid cancer has also been documented in Ukraine, and to a much lesser extent in the Russian Federation. Epidemiological studies indicate an increased frequency of benign thyroid nodules and thyroid autoimmunity.

The important medical and social impact of the thyroid consequences of the Chernobyl accident prompted the cooperation between the affected countries and the European Commission aimed to provide an adequate and qualified health support for the people suffering from thyroid cancer and other thyroid disorders. The present report summarizes the activities and achievements of our EC funded projects aimed to optimize the diagnosis, treatment and rehabilitation of patients with thyroid cancer and other thyroid diseases.

Summary

The association between radiation exposure and papillary thyroid carcinoma has been observed several years after external irradiation to the head and the neck in subjects treated for various non-thyroidal disorders. The Chernobyl nuclear reactor accident, has clearly shown that also exposure to radioactive fall-out may cause an increase in the prevalence of thyroid carcinoma. Starting from 1990, more than 800 thyroid cancers have been observed in children less than 15 years old, living in the most contaminated areas of Belarus, Ukraine and, to a lesser extent, of the Russian Federation.

A comparison between clinical and epidemiological features of childhood thyroid carcinomas, diagnosed in Belarus after the Chernobyl accident and naturally occurring thyroid carcinoma of the same age group observed in Italy and in France, shows that the post-Chernobyl thyroid carcinomas were much less influenced by gender, were virtually always papillary (solid and follicular variants), had higher aggressiveness at presentation, and were more frequently associated with thyroid autoimmunity. Gene rearrangements, involving the RET proto-oncogene (less frequently TRK), have been demonstrated as causative event specific for papillary cancer. Much higher rates of RET activation (nearly 70%) have been found in post-Chernobyl papillary thyroid carcinomas. The prevalence of specific types of rearrangement differs in sporadic tumors (mainly RET/PTC 1) with respect to radiation-induced neoplasm (mainly RET/PTC 3).

When appropriately treated, with the combination of surgery, radioiodine and hormone suppressive therapy, post-Cheernobyl childhood thyroid cancer is a curable disease, with very high cure rate even in the presence of distant metastases.

In addition to thyroid cancer, radiation-induced thyroid diseases include benign thyroid nodules, hypothyroidism and autoimmune thyroiditis with or without thyroid insufficiency. Epidemiological and clinical studies evaluating thyroid autoimmune phenomena in normal subjects exposed to radiations after the Chernobyl accident, demonstrated an increased prevalence of circulating anti-thyroid antibodies, not associated with significant thyroid dysfunction, although the possibility of later development of clinical thyroid autoimmune diseases, especially hypothyroidism, is very likely.

Future screening programs for thyroid diseases in the population at risky, should be focused not only on the detection of thyroid nodules and cancer, but also on the development of thyroid autoimmune diseases.

INTRODUCTION

Both external and internal ionizing radiation have been linked to the development of thyroid carcinoma and thyroid autoimmunity. In particular, ionizing radiation is recognized as the main risk factor for developing thyroid carcinoma especially when radiation exposure occurs during childhood. Both an increased incidence of thyroid carcinoma, mainly of the papillary histotype, and, to a lesser extent, of autoimmune phenomena have been observed several years after external irradiation to the head and the neck in subjects treated for various non-thyroidal disorders (1-4), in atomic bomb survivors in Japan (5), and in residents of the Marshall Island exposed to radiation during the testing of hydrogen bombs (6).

1. POST-CHERNOBYL THYROID CANCER.

The Chernobyl nuclear reactor accident has clearly shown that exposure to radioactive fall-out was the cause of an enormous increase in the prevalence of childhood thyroid carcinoma (7-11). The size of this increase, the geographical and the temporal distribution of the cases strongly suggest that the increased incidence of thyroid cancer is due to radiation exposure and, most likely, to the huge amount of iodine radioisotopes released by the damaged Chernobyl reactor, which includes 131-I and other short-lived iodine isotopes (12). A state of endemic iodine deficiency and the absence of immediate iodine prophylaxis might have further contributed to high radiation exposure of the thyroid, especially in children, in whom the final radiation dose per gram of tissue is much more important with respect to adults (13).

Following diagnostic or therapeutic administration of radioiodine isotopes (131-I), no evidence of an increased relative risk of thyroid carcinoma has been detected (14,15), at least in adults. No evidence of an increased risk was observed in children, but admittedly the relatively low number of children submitted to these treatment modalities does not allow to exclude a risk albeit small.

Clinical features of post-Chernobyl thyroid carcinomas.

An increase in the number of thyroid carcinomas in children and adolescents after the Chernobyl accident has been observed in the south of Belarus, in the north of Ukraine starting from 1990 and in the regions of Briansk and Kaluga (south of Russian Federation) since 1994. A relative increase in the number of thyroid cancers has been observed even in adults from Belarus and Ukraine. This increase is much less important than that observed in children and it is likely due to the greater attention at thyroid diseases after the nuclear accident.

About 800 thyroid cancers have been observed in children less than 15 years old living in the most contaminated areas. Such data correspond to an increase from 0.03 to 3 thyroid cancers per 100,000 children per year. About 98% of these thyroid tumors have been observed in children less than 10 years of age and 65% in children less than 5 years at the time of the accident. Thyroid cancer cases were also registered in some children who were already generated, but still in the uterus, at the time of the accident.

The yearly distribution of new cases shows that the increase in children reached its peak in 1993, with a trend to a "plateau" in the following years (16). It is also apparent that the patients of the 5-years-or-less age group at the time of the accident, accounted for the majority of the cases in each year of observation, while a decreasing trend in the number of thyroid cancer cases was observed in the subjects who were 9 years old or more at the time of the accident, with no new cases being observed in 1995.

The mean latency period between radiation exposure and diagnosis is about 9-10 years, with a similar trend in children and adolescents, shorter than that found after external thyroid radiation (2,3).

A comparison between clinical and epidemiological features of thyroid carcinomas, diagnosed in Belarus after the Chernobyl accident and those of 369 children and adolescents that in the past 20 years were followed for thyroid carcinoma in Italy and in France, shows that the post-Chernobyl thyroid carcinomas were much less influenced by gender, the female-to-male ratio being significantly higher in Italy and in France (2.5/1) compared with Belarus patients (1.6/1). Furthermore, most of the Belarussian cases (87.9%) were diagnosed before the age of 15, while the distribution of cases in Italy and France increases progressively with the age, the majority (57.4%) of the patients being diagnosed after the age of 14.

Morphological analysis of post-Chernobyl childhood thyroid carcinomas showed that the large majority of them are papillary carcinomas, very few being of the follicular histotype (16-18). Among the papillary type, many (33%) are of the solid and follicular variants (18). Focal micropapillary hyperplasia is frequently found in post-Chernobyl thyroid glands (19). Post-Chernobyl thyroid cancers showed a great aggressiveness since the presentation of the disease. A comparison with naturally occurring thyroid carcinomas in Italy and France showed a significantly higher extrathyroidal extension in Belarussian children (49.1 %) with respect to age-matched cases in Italy and France (24.9%). A frequent association of post-Chernobyl tumors with lymphocytic infiltration and humoral thyroid autoimmunity has also been reported (16).

Molecular biology investigation shows some peculiarities. Ras and p53 genes are not involved in the pathogenesis of these tumors while rearrangements of the RET proto-oncogene are found in nearly 70% of the cases, a percentage higher than that observed in

non-irradiated papillary thyroid carcinomas (20-23). The type of RET rearrangements differs in post-Chernobyl cases and in spontaneous tumors (24). RET/PTC3 is the form more frequently expressed in radiation-induced tumors, particularly in the solid variants, while RET/PTC1 is predominant in spontaneous tumors and in the classical papillary variant (23). These findings suggest that RET/PTC3 mutation could be specifically related to the radiation effect, although the young age of affected subjects *per se* might be a contributing factor, as demonstrated by the higher incidence of RET rearrangements found in children and adolescents with papillary thyroid cancer not exposed to radiation (25).

Treatment of radiation-induced differentiated thyroid cancer.

The initial treatment of differentiated thyroid cancer in adults, children and adolescents, is surgery. Although some controversy still exists on the extent of thyroid surgery to be performed, we are in favor of the so called "near-total thyroidectomy", a procedure intended to leave no more than 2-3 gr. of thyroid tissue. Surgery should be performed by an experienced surgeon who can perform this operation with minimal morbidity. Both permanent hypoparathyroidism and vocal cord palsy are almost absent in the hands of an experienced surgeon, and should not be advocated as reasons against total or near-total thyroidectomy. The reasons for total thyroidectomy are:

a) to allow the diagnosis and treatment of metastatic lesions with radioactive iodine;

b) to use serum thyroglobulin as a sensitive indicator of recurrent or persistent disease;

c) to remove multifocal disease, thus decreasing the rate of local recurrence (26, 27).

Four-six weeks after surgery all patients should be treated with radioiodine for ablation of any post-surgical residual thyroid tissues. A 131-I Whole Body Scan (WBS) is performed 3-5 days after the administration of this ablative dose, in order to search local or distant metastases. Serum thyroglobulin (Tg), a specific marker of residual or metastatic thyroid tissue in differentiated thyroid cancer, is also measured at this stage. The positively of WBS and/or the finding of elevated serum Tg levels are the indications to treat the patient with a therapeutic dose of 131-I (usually 1 mCi/Kg of body weight in children). In case of persistent disease after surgery and residue ablation, WBS and 131-I therapy are repeated at intervals of 8-12 months. The aim of this therapy is to achieve a definitive cure, demonstrated by negative WBS and undetectable serum Tg concentrations off L-thyroxin (L-T4).

The other essential step in the treatment of childhood differentiated thyroid cancer is hormonal therapy. Cancer cells of the follicular thyroid epithelium are, at least in part, TSH dependent for their function and growth. Thus, suppression of TSH (thyroid hormone suppressive therapy) is part of the therapeutic strategy. The drug of choice is L-T4 and the effective dosage needed to suppress endogenous TSH in children is between 2.2-2.8 mg/Kg of body weight. To avoid overtreatment (subclinic hyperthyroidism) an attempt should be made to use the smallest dose of L-T4 necessary to suppress TSH secretion, while determining a normal level of circulating thyroid hormones (FT4, FT3). Monitoring of the effectiveness of the therapy is performed by measuring serum TSH, FT4 and FT3 every six months. Following these indications L-T4 suppressive therapy is safe in children and adolescents, and does not affects the normal growth and

development. When appropriately treated, differentiated thyroid cancer is a curable disease, with very high cure rate even in the presence of distant metastases.

2. RADIATION EXPOSURE AND THYROID AUTOIMMUNITY

Nuclear accidents represent a major public health concern, because of injuries to the general population deriving from the exposure to ionizing radiation. In these accidents, a small number of individuals may be exposed to very high direct irradiation, which is often lethal, while large groups of subjects, often residing away from the site of the accident (far field), are exposed to relatively low doses, mostly deriving from ingestion or inhalation of radioactive isotopes dispersed in the environment.

The occurrence of thyroid autoimmunity following exposure of the thyroid gland to radiation has been reported, and may have implication in population exposed to accidental radioactive contamination. Exposure of the thyroid to both internal or external radiation may trigger an autoimmune reaction.

The ability of the thyroid to concentrate radioiodide and its anatomic position in the anterior neck account for its peculiar susceptibility to exposure to ionizing radiation. On the other hand, the thyroid gland is a common target of autoimmune reaction and autoimmune thyroid diseases are frequent in the general population. Both external radiation from X-rays and internal radiation from radioisotopes of iodide, which give rise to gamma-radiation and to beta or beta-like radiation, may involve the thyroid gland, and must be considered in regard to thyroid autoimmunity.

Internal radiation and thyroid autoimmunity

After ^{131}I therapy for hyperthyroidism in Graves' disease the dose of radiation absorbed by the thyroid is in the order of 7000-10000 rads. In these patients, immunologic studies performed after ^{131}I administration have shown a transient increase of thyroid antibodies, which may include anti-thyroglobulin antibodies (AbTg), anti-thyroperoxidase antibodies (AbTPO) and TSH-receptor antibody (TRAb) (28-30). The elevation occurs 2 to 3 months after treatment and is followed in the majority of patients by a subsequent decline. Only a few patients developed a sustained increase of TSH-receptor antibody after ^{131}I, which may be responsible for an exacerbation of the disease. The changes in humoral immunity are specific for the gland, since the increase in thyroid antibodies is not accompanied by variations in parietal cell or cell nuclei antibodies (30).

n the past, the *de novo* appearance of TPOAb and/or TgAb at low titer was reported in patient with no thyroid disease given ^{131}I for angina. No such increase in thyroid antibodies is observed after intensive local radiation of other tissues (uterus) suggesting that the increase in thyroid antibodies is not due to a general stimulation of the antibody-producing system (30).

Changes in thyroid autoimmunity after ^{131}I therapy have been attributed to the release of thyroid autoantigens as a result of radiation damage to the gland (2). Selective depletion of intrathyroidal T-suppressor cells which are more radiosensitive than T-helper cells may also play a role (31).

The exacerbation of thyroid autoimmunity after ^{131}I may contribute to the high cumulative incidence of hypothyroidism which is observed in hyperthyroid Graves' patients treated with radioiodine (28). A significant high incidence of histologic patterns resembling Hashimoto's thyroiditis is found in Graves' glands irradiated with [131]I (28).

To our knowledge the effect on thyroid autoimmunity produced by exposure to diagnostic ^{131}I doses, has not been studied in humans. Thyroiditis with lymphocytic infiltration and oxyphil epithelial cells has been observed in rats after low doses of radioiodine (32).

Data on the effect of environmental exposure to radioactive isotopes of iodine derive from the experience in the Marshall Islands population who was accidentally exposed to the fallout from the hydrogen bomb explosion at Bikini Atoll in 1954 and in the survivors of the atomic bomb explosion in Hiroshima and Nagasaki (5,33). Sixteen percent of the Marshallese developed hypothyroidism that was much more marked in children than in adults (33). The incidence of hypoparathyrodism in this population was much greater than would be predicted from the calculated radiation dose and this excess can be probably attributed to the contribution of short lived isotopes such as [132]I, [133]I and [135]I, whose biological effectiveness is estimated to be 4 to 10 times more destructive per rad than that of [131]I. Thyroid autoimmunity was apparently not involved in the development of hypothyroidism, since TPOAb and TgAb were not detected in sera from exposed subjects. On the other hand, in survivors of the direct radiation exposure from atomic bombs in Hiroshima and Nagasaki, the prevalence of hypothyroidism due to Hashimoto's thyroiditis was significantly higher in the population exposed than in controls (5).

External radiation and thyroid autoimmunity

The development of endocrine ophthalmopathy with or without clinical hyperthyroidism has been reported in occasional patents given therapeutic X-radiation to the neck 18 months to 10 years previously for nonthyroid neoplastic disease, which included Hodgkin's disease, lymphoma, breast cancer, laryngeal carcinoma and nasopharyngeal epithelioma. In these cases the radiation dose delivered to the thyroid was in the range of 3000-5000 rads. High levels of serum TgAb and/or TPOAb were found at the time when ophthalmopathy appeared, and thyroid stimulating antibodies were detected in 3 out of 6 patients tested.

A number of observations have been made concerning the consequences of therapeutical X-radiation to apparently normal thyroid glands. A high incidence of subclinical or clinical hypothyroidism has been found in patients with Hodgkin's or non-Hodgkin's lymphoma who received radiation therapy to the neck at a dose ranging from 1500 to 4500 rads, which are far below that usually required to destroy the normal thyroid gland (4). In one series, the occurrence of thyroid antibodies in nearly 50% of hypothyroid patients suggested that radiation-induced autoimmune thyroiditis contributed to thyroid dysfunction. The post-radiation appearance of clinical Hashimoto's thyroiditis or myxedema was also described. Autoimmune thyroid disease was also reported in adult patients submitted to low-dose (300-600 rads) radiation to the head and neck during childhood.

Iodine and thyroid autoimmunity

Both iodine deficiency and iodine excess may play a role in thyroid autoimmunity. This is particularly relevant to the present discussion since iodine-deficient areas are present in

Belarus and because iodine prophylaxis was performed in some districts of Belarus after the Chernobyl accident. This procedure reduces thyroid radio-iodine uptake and is currently recommended as a preventive measure for radiation-induced thyroid damage after a nuclear accident.

Autoimmunity in post-Chernobyl Belarus children and adolescents

To evaluate thyroid autoimmune phenomena in patients exposed to radiation after the Chernobyl accident, we studied 287/3105 (9.2%) children (age at accident 0-9 yr.) living in Hoiniki village, south of Gomel, which was contaminated by the post-Chernobyl radioactive fall-out (5.4 Ci/Km^2 of Cesium) and a control group of 208/5273 (3.9%) children of the same age living in Braslav, in the province of Vitebsk, which was not contaminated (<0.1 Ci/Km^2 of Cesium) (34). All children were randomly selected during periodical screening programs in the schools from 1992 to 1994, 6-8 years after the nuclear accident. The Hoiniki group was composed of 144 males and 143 females ranging in age between 6-17 yr. (mean: 11.6±3.2 yr.) at the time of the study. The Braslav group included 95 males and 113 females, aged 7-18 yr. (mean: 13±2.6 yr.). At the time of the accident their mean age was 5.4±2.8 years (range: <1-10) in Hoiniki group (13 subjects were in uterus) and 6.5±2.5 years (range: <1-12) in the Braslav group. In all patients we studied thyroid function (serum FT3, FT4 and TSH), and humoral thyroid auto-immunity: anti-thyroglobulin antibodies (AbTg) and anti-thyroperoxidase antibodies (AbTPO).

In the Hoiniki group the mean value of AbTg was 9.5±35.3 U/ml (range: 4.1-426) not different compared to the Braslav group (7.2±14.3 U/ml); mean values for AbTPO (11.3±29.8 U/ml) in Hoiniki were significantly higher (p=0.0008) than those found in Braslav (4.2±4.3 U/ml). The prevalence of positive AbTg and/or AbTPO was significantly higher (p=0.0001) in subjects living in Honiki (55/287=19.1%) than in those living in Braslav (8/208=3.8%). A significant difference was still found when analyzing the prevalence of AbTg alone (8.3% in Hoiniki vs 2.8% in Braslav; p=0.02), or AbTPO alone (16.7% vs 1.9%; p=0.0001), or AbTg and AbTPO (6% vs 1%; p=0.02). The prevalence of anti-thyroid antibodies was not different between males and females in the Hoiniki group; but, in both sex, it was significantly higher compared to the Braslav group (males: p<0.01; females: p<0.0005). The prevalence of circulating antibodies in the contaminated group started to increase in subjects who, at the time at the accident, were in uterus or newborns (15.7%), continued after that, and had a further increase in children 8-9 year old (30.1%). In the control group a very modest prevalence of positive antibodies was found, starting in the second year of age and remaining constant after that. Differences were not found between mean values of FT3, FT4, TSH in the two groups. Five children in Hoiniki and 6 in Braslav had sub-clinicalhypothyroidism and one children in Hoiniki had slightly elevated FT3 levels with suppressed TSH. All of them had no anti-thyroid antibody.

3. CONCLUSION

In conclusion, our collaborative program devoted to optimize the diagnosis, treatment and rehabilitation of patients with thyroid cancer and other thyroid diseases helped clariphying the epidemiological and clinical features of post-Chernobyl thyroid carcinoma and demonstrated that post-Chernobyl radiation fall-out has been also the cause of an increased incidence of thyroid autoimmunity.

Specific achievement of the collaborative program may be summarized as follows:

I. definition of common protocols for the diagnosis and treatment of thyroid cancer and other thyroid disorders;

II. implementation of procedures for the optimization of diagnosis, treatment, rehabilitation and follow-up of patients

III. treatment, follow-up and rehabilitation of patients with thyroid cancer and other disorders;

IV. training program for physicians and other health personnel in charge of the patients;

V. cooperation for providing appropriate drugs and treatment facilities.

In view of the continous occurrence of thyroid disorders in the population exposed the radioactive fall-out, future activities need to be implemented as follows:

I. ensure screening of subjects at risk for the early detection of thyroid cancer, thyroid autoimmunity and other thyroid diseases;

II. provide medical and technical expertise within the framework of a continuous education program;

III. provide an effective therapy and follow-up of patients with thyroid cancer and other thyroid diseases;

IV. critical assessment of the results within a program of scientific cooperation.

Partners: F. Delange (Bruxelles); C. Reiners (Essen);
M. Schlumberger (Villejuif)

Project INCO-Copernicus I (IC15 CT 96 0310)

Investigation on thyroid cancer and other thyroid disorders in CIS countries affected by the post-Chernobyl nuclear accident
Coordinators: A. Pinchera, F. Pacini (Pisa);
EU Partners: M. Schlumberger (Villejuif)
CIS Partners: E.P. Demidchik (Minsk); E. Parshkov (Obninsk);
T. Vorontsova (Minsk); N. Tronko (Kiev)

Project INCO-Copernicus II (IC15 CT98 0314)

Screening program for the assessment of the prevalence of clinical and sub-clinical thyroid autoimmunity and insulin-dependent diabetes mellitus (IDDM) in contaminated territories of CIS countries and Western Europe
Coordinators: A. Pinchera, F. Pacini (Pisa);
EU Partners: S. Mariotti (Cagliari); G. Bottazzo (London);
U. Feldt-Rasmussen (Copenhagen)
CIS Partners: A. Arinchia (Minsk); L. Kolesnikova (Irkntsk);
T. Mokhort (Minsk); A. Tsyb (Obninsk); N. Tronko (Kiev)

Project TACIS

"Technical Assistance to the Commonwealth of Indipendent States" for training of medical personnel"
Chairman: M. Schlumberger (Villejuif)
Partners: A. Pinchera (Pisa); E.D. Williams(Cambridge);
C. Reiners (Esssen); J. Orgiazzi (Lyon); J. Dumont (Bruxelles);
R. Vigneri (Catania); J.P. Travagli (Villejuif)

Project ECHO

"European Community Humanitarian Office"for provision of special equipment and medical supplies for the treatment of childhood thyroid cancer.
Advisors: Western European experts.

References

1) Schneider AB, Shore-Freedman E, Weinstein RA. Radiation induced thyroid and other head and neck tumors: occurrence of multiple tumors and analysis of risk factors. *J Clin Endocrinol Metab* 1986; **63**: 107-112.

2) Favus MJ, Schneider AB, Stachura ME, et al. Thyroid cancer occurring as a late consequence of head-and-neck irradiation. Evaluation of 1056 patients. *N Engl J Med* 1976; **294** : 1019-1025.

3) Shore RE. Issues and epidemiological evidence regarding radiation-induced thyroid cancer. *Radiat Res* 1992; **131** : 98-111.

4) Hancock SL, Cox RS, McDougall IR. Thyroid disease after treatment of Hodgkin's disease. *N Eng J Med* 1991; **325**:599-605.

5) Nagataki S, Shibata Y, Inoue S, Yokoyama N, Izumi M, Shimaoka K. Thyroid disease among atomic bomb survivors in Nagasaki. *JAMA* 1994; **272**: 364-370.

6) Conrad RA, Pegia DE, Larson PR, et al. Review of medical findings in a Marshallese population twenty-six years after accidental exposure to radio-active fallout. BNL 51261, NTIS, January 1980; 1-138.

7) Baverstock K, Egloff B, Pinchera A, Ruchti C, Williams D. Thyroid cancer after Chernobyl. *Nature* 1992; **359**: 21.

8) Demidchik E, Kazakov VS, Astakhova LN, Okeanov AE, Demidchik YuE. Thyroid cancer in children after the Chernobyl accident: clinical and epidemiological evaluation of 251 cases in the Republic of Belarus. In: Nagataki S, ed. Nagasaki Symp., Chernobyl: Update and Future. Amsterdam 1994: Excerpta Medica, Elsevier Press; 21-30.

9) Kazakov US, Demidchik E, Astakhova LN. Thyroid cancer after Chernobyl. *Nature* 1992; **359** : 21.

10) Sobolev B, Likhtarev I, Kairo I, Tronko N, Oleynik V, Bogdanova T. Radiation risk assessment of the thyroid cancer in Ukrainian children exposed due to Chernobyl. In: Karaoglou A, Desmet G, Kelly GN, Menzel HG, eds. The Radiological Consequences of the Chernobyl Accident. ERU 16544 EN. Luxembourg 1996: European Commission: 741-748.

11) StSjazhko VA, Tsyb AF, Tronko ND, et al. Childood thyroid cancer since accident at Chernobyl. *Br Med J* 1995; **310** : 801.

12) Williams D, Pinchera A, Karaoglou A, Chadwick KH, eds. Thyroid cancer in children living near Chernobyl. Report EUR 15248 EN, Office for Official Publications of the European Communities, Luxembourg 1993; 1-108.

13) Dumont JE, Corvilain B, Coclet J,Raspe E, Reuse S. Recent progress in fundamental thyroidolgy with rilevance to the prevention of medical consequences of a nuclear accident. In: Rubery E, Smales E, eds. Iodine prophylaxis following nuclear accident. WHO/CEC Workshop, July 1988; 33-37.

14) Globel B, Globel H, Oberhausen E. Epidemiologic studies on patients with iodine-131 diagnostic and therapy. In: Kaul A., Neider R., Pensko J. at al., eds. Radiation Risk Protection, vol. II°. International Radiation Protection Association. Koln: Fachverband fur Strahlenschutz e. v., 1984; 565-568.

15) Hall P, Mattsson A, Boice JD, JR. Thyroid cancer after diagnostic administration of iodine-131. *Radiat Res* 1996; **145** : 86-92.

16) Pacini F, Vorontsova T, Demidchik E.P, et al. Post-Chernobyl thyroid carcinoma in Belarus children and adolescents: comparison with naturally occurring thyroid carcinoma in Italy and France. *J Clin Endocrinol Metab* 1997; **82** : 3563-3569.

17) Williams ED, Cherstvoy E, Egloff B, et al. Interaction of pathology and molecular characterization of thyroid cancers. In "The radiological consequences of the Chernobyl accident", (Eds: A. Karaoglou, G. Desmet, GN Kelly, HG. Menzel), ERU 16544 EN, Luxembourg 1996; 699-714.

18) Nikiforov Y and Gnepp DR. Pediatric thyroid cancer after the Chernobyl disaster. Pathomorphologic study of 84 cases (1991-1992) from the Republic of Belarus. *Cancer* 1994; **74** : 748-766.

19) Nikiforov Y, Gnepp DR, Fagin JA. Thyroid lesions in children and adolescents after the Chernobyl disaster: implcations for the study of radiation tumorigenesis. *J Clin Endocrinol Metab* 1996; **81**: 9-14.

20) Fugazzola L, Pilotti S, Pinchera A, et al. Oncogenic rearrangements of the RET proto-oncogene in papillary thyroid carcinomas from children exposed to the Chernobyl nuclear accident. *Cancer Res* 1995; **55**: 5617-5620.

21) Klugbauer S, Lengfelder E, Demidchik EP, Rabes H.M. High prevalence of RET rearrangement in thyroid tumors of children from Belarus after the Chernobyl reactor accident. *Oncogene* 1995; **11:** 2459-2467.

22) Takahashi M, Ritz J, Cooper GM. Activation of a novel human trasforming gene, ret, by DNA rearrangement. *Cell* 1985; 42: 581-588.

23) Nikiforov YE, Rowland JM, Bove KE, Monforte-Munoz H, Fagin JA. Distinct pattern of ret oncogene rearrangements in morphological variants of radiation-induced and sporadic thyroid papillary carcinomas in children.. *Cancer Res* 1997; **57**: 1690-1694.

24) Santoro M, Carlomagno F, Hay ID, et al. Ret oncogene activation in human thyroid neoplasms is restricted to the papillary cancer subtype. *J Clin Invest* 1992; **89**: 1517-1522.

25) Bongarzone I, Fugazzola L, Vigneri P, et al. Age-related activation of the thyrosine kinase receptor protooncogenes RET and NTRK1 in papillary thyroid carcinoma. *J Clin Endocrinol Metab* 1996, **81**: 2006-2009.

26) Witt TR, Meng RL, Economou SE, Southwick HW. The approach to the irradiated thyroid. *Surg Clin North Amer* 1979; **59** : 45-63.

27) Harness J, Thompson NW, McLeod MK, Pasieka JL, Fukuuchi A. Differentiated thyroid carcinoma in children and adolescents. *World J Surg* 1992; **16**: 547-554.

28) Williams ED. Biological effects of radiation on the thyroid. In: Braverman LE, Utiger RD (Eds), The thyroid. Lippincott Co., Philadelphia 1991, 421.

29) Pinchera A, Liberti P, Martino E. et al. Effects of antithyroid therapy on the long-acting thyroid stimulator and anti-thyroglobulin antibody. *J Clin Endocrinol Metab* 1969, **29**:231.

30) Jonsson J, Einhorn N, Fagraeus A, Einhorn J. Organ antibodies after local irradiation. *Radiology* 1968, **90**:536.

31) Teng W-P, Stark R, Munro AJ, McHardy Young S, Borysiewicz LK, Weetmann AP. Peripheral blood T cell activation after radioiodine treatment for Graves' disease. *Acta Endocrinol* 1990, **122**:233.

32) Potter JD, Lindsay S, Chaikoff IL. Induction of neoplasia in rat thyroid glands by low doses of radioiodine. *Arch Pathol* 1960, **69**:31.

33) Larsen PR, Conard RA, Knudsen K. Thyroid hypofunction after exposure to fallout from a hydrogen bomb explosion. *JAMA* 1982, **247**:1571.

34) Pacini F, Vorontsova T, Molinaro E. et al. Increased prevalence of thyroid autoantibodies in Belarus children and adolescents exposed to the Chernobyl radioactive fallout. *Lancet* 1998; **352**:763-6.

SCIENTIFIC SEMINAR ON THYROID DISEASES AND EXPOSURE TO IONISING RADIATION : LESSONS LEARNED FOLLOWING THE CHERNOBYL ACCIDENT

Conclusions and potential implications

Dr P. SMEESTERS

INTRODUCTION

This document presents the main conclusions and potential implications of the Scientific Seminar on Thyroid Diseases and Exposure to ionising Radiation held in Luxembourg on 26 November 1998. While it is not intended to report, in an exhaustive manner, all the opinions that were expressed by the speakers or by the audience, it will take into account the discussions that found place during the subsequent meeting of the « Article 31 » Group of experts on 27 November 1998. The content of the document has been discussed within the RIHSS (Research Implications on Health Safety Standards) Working Party[*] and has been submitted for advice to the lecturers, whose remarks were taken into account as far as possible, subject sometimes to the final arbitration of the RIHSS Working Party.

1. RIHSS SEMINARS : RATIONALE

The RIHSS Working Party of the « Article 31 » Group of experts was set up with the task to help to identify the potential implications of recent research results or new data analysis on the European Basic Safety Standards (B.S.S.), Guidance's and Recommendations.

The adopted approach is the following: on the basis of the input from DG XII (Science, Research and Development) and of the information transmitted by the individual experts of the Art. 31 Group, the Working Party proposes yearly to the Art. 31 Group relevant themes that could be discussed during a subsequent seminar. After selection of a theme and approval of a draft program, the WP deals with the practical organization. The seminars involve invited speakers, mainly leading experts, who are asked to clearly synthesize the state-of-the-art in the field, with special attention to new information, together with additional experts, who are pointed out in their own country by the Art. 31 experts and act as peer reviewers. The seminars are convened by the Commission the day before an Art. 31 Group meeting. It gives the Art. 31 experts the opportunity to discuss the potential implications of consolidated scientific results.

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[*] The members of the RIHSS Working Party who took part in the redaction of this document were: R. CLARKE (Art. 31), J. PIECHOWSKI (Art. 31), P. SMEESTERS (Art. 31, chairman of the WP), A. SUSANNA (Art. 31), V. CIANI (DG XI), K. CHADWICK (DG XII) and A. KARAOGLOU (DG XII).

2. RADIATION-INDUCED THYROID DISEASES : GROUND FOR THEME SELECTION, BACKGROUND, CONCLUSIONS OF THE 1995-1996 INTERNATIONAL CONFERENCES AND QUESTIONS TO THE INVITED SPEAKERS

2.1. Theme selection

The question of radiation-induced thyroid diseases has been of concern in recent years as a result of the observations in the populations living near Chernobyl. Several international Conferences[*] took place in 1995-1996 around the tenth anniversary of the nuclear accident. In spite of a wide agreement on the evaluation of the Chernobyl data, some fundamental questions remained open. In July 1998, a scientific seminar on this topic was held in Cambridge[**], the results of which can now be taken into account.

Potential repercussions at the European level are numerous, including revision of risk estimations of radiation-induced thyroid cancer, thyroid tissue weighting factor, emergency intervention levels, maximum permitted levels of radioactive iodine contamination of foodstuffs and iodine prophylaxis.

2.2. Background

The susceptibility of the thyroid to radiation-induced cancer has been recognized in many studies, particularly for external irradiation and for exposure in childhood (Japanese atomic bomb survivors, infants exposed to therapeutic x-rays for several benign diseases,…).

Although mortality is low, the risk coefficients for radiation-induced thyroid cancer incidence are rather high: the lifetime risk (population of all ages, low-LET radiation) was evaluated by the ICRP at 0.8×10^{-2} Sv^{-1} (ICRP: Publication 60), while the risk estimates of the NCRP (NCRP : Report 80) for a population of children are consistent with a lifetime risk of 1.5×10^{-2} Gy^{-1}.

As a rule, the data were well fitted by a *linear* dose-response function, with some statistically significant points down to about 100 mSv.

The risk appears 5 to 10 years after the exposure and persists for many years: in the pooled analysis of E. RON and coll. (Radiat. Res. 141: 259-277, 1995), the Excess Relative Risk for childhood exposures began to decline 30 years after exposure but was still existing after 40 years.

As many studies are based on childhood exposures and the follow-up period is insufficient, there is remaining uncertainty on which projection model is the most appropriate.

Epidemiological studies based on *internal* exposures, mainly patients exposed to ^{131}I for medical reasons, provided essentially *negative* information with regard to thyroid cancer

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[*] WHO, Genève, 1995 ; EC, IAEA, WHO, Vienna, 1996 ; EC, Belarus, Russian and Ukrainian Ministries, Minsk, 1996.

[**] University of Cambridge, EC, DOE, NCI, Cambridge, 1998.

induction, which suggested that the risk is (much) lower than after external irradiation. Nevertheless, most of the available data were based on exposures of *adults.*

2.3. Chernobyl observations (as reported during the 1995-1996 international conferences)

Ten years after the accident, the most striking, unexpected and least questionable effect was found to be a significant increase of thyroid cancer in children, in the areas most exposed to the initial radioactive clouds. Young children seem particularly vulnerable and were affected by thyroid cancers of an aggressive or invasive nature and with a short latency period. The age distribution analysis of the thyroid cancers suggested that the relative risk for the children who were the youngest at the time of the exposure is much higher than for older children and especially much more pronounced than was predicted on the basis of previous observations.

Some increase in the incidence of adult thyroid cancer was also observed, but could be the result of better screening.

A higher prevalence of anti-thyroid antibodies was found in children living in contaminated areas, without at this time clinical hypothyroidism.

2.4. Open questions

Although there is little doubt on the relation between the Chernobyl accident and the increase of the incidence of childhood thyroid cancer in the affected areas, some important residual issues are still under discussion.

The speakers were invited in advance to address some of those such as:

- the differences in age-specific risk coefficients and temporal pattern for the appearance of the radiation-induced thyroid cancers;

- the magnitude of the risk of radiation-induced thyroid cancer in *adults* ;

- the role of *host susceptibility factors* other than age (ethnic origin, diet,…) ;

- the pathogenic mechanism of the induction of thyroid cancers by ionising radiation and ,in particular, the relative effectiveness of *external v. internal* exposure and of iodine 131 v. other *short-lived* iodine isotopes ; this includes the discussion of the possible role of dose rates and of the apparent discrepancies between the Chernobyl data and the observations in patients treated with radioactive iodine;

- the clinical significance and the dose-effect relation of radiation-induced *autoimmune thyroiditis* ;

- the results of the studies on *thyroid dose reconstruction* following the Chernobyl accident ;

- the influence of iodine deficiency and iodine supplementation for the recommendations on *iodine prophylaxis*.

3. MAIN CONCLUSIONS OF THE PRESENTATIONS AND OF THE SUBSEQUENT DISCUSSION

The presentations and discussions confirm the conclusions drawn during the 1995-1996 conferences:

- the large rise in the incidence of confirmed cases of thyroid carcinoma in children exposed to fallout from the Chernobyl nuclear accident ,

- the correlation of incidence and extent of fallout ,

- the rapid drop in incidence to near normal figures in children born more than a few months after the accident,

all of which combine to show a causal relation between exposure and carcinogenesis.

3.1. Age-at-exposure effect in radiation-induced thyroid cancers

The most controversial issue was the magnitude of the age at exposure effect and whether or not the Chernobyl observations are in good agreement with previously published data on external and internal exposures.

According to **Williams**, the comparison of the Observed/Expected ratio (O/E: *relative risk* or RR) of thyroid cancer incidence (combined Belarus cases between 1990 and 1997 inclusive) in cohorts of children of the same age at exposure (those under 1 at exposure, those between 1 and 2, etc) show _very high_ figures (O/E ~180) for the *youngest* cohort and a smooth drop to a figure of O/E~20 for those aged 8 at exposure.

These ratios compare Belarus with England and Wales figures which are in the lower international range. Choosing another country as baseline would affect the scale of the increase but not the relative age related sensitivity.

The difference between these observations and the previous studies, where the relative risk in the 0-4 and 10-14 age at exposure cohorts was a ratio around 5 :1 (E. Ron et al., op. cit.) may be related to a) the higher dose to younger children from the same environmental exposure to radioiodine, while the 5 :1 ratio is based on X-ray studies, and b) the more extended follow-up in the X-ray studies. Relevant to this are possible recent indications that the youngest cohort at exposure to Chernobyl may have reached a peak relative risk, but it is too early to form a definite conclusion and further study is needed.

On this basis, it is difficult to predict the future development of the incidence of thyroid cancer in the exposed population (lifetime incidence); moreover, an increase in follicular carcinoma (with a longer latent period) may yet occur, and this is perhaps indicated by the observed increase in the incidence of thyroid nodules and adenomas in children in Gomel.

On the basis of an aggregated study using *average thyroid doses* in more than 5000 settlements in the contaminated areas and thyroid cancers in the birth cohort 1971-1986 (*0-15 years at exposure cohort* : 2 328 000 people), estimations of *excess absolute risk* (EAR : number of excess cases per 10^4 person-year) of thyroid cancer per unit thyroid dose are reported by **Goulko and Jacob**. The excess risk was shown to be a linear

function of the dose. These estimates are judged <u>comparable</u> (2 times smaller) to the risk previously reported after *external* exposures (Ron's pooled figures,op.cit .).

The use of group doses, instead of individual dose estimates, to calculate risk estimates was a controversial point . According to Jacob, the range of average thyroid doses between the considered settlements is considerably larger than the range of individual doses in the single settlements (Jacob et al, Nature, 392, 31-32, 1998), which justify using average thyroid doses. However the presence of confounding factors cannot be excluded.

As the observation in the Chernobyl cohort is only 5-9 years after the exposure and the external exposure studies cover several tens of years, the comparability of the two sets of results was also challenged, as was the validity of the conclusion for the youngest cohort (0-5 years at exposure) which could be more sensitive to the induction of thyroid cancer by radiation.

The paper by **Cardis, Amoros and Kesminiene** gives predictions of radiation-induced thyroid cancers over lifetime –as well as over the first ten years after the accident- for children exposed before the age of 5 (*0-5 years at exposure cohort)*, using the best available *relative risk* estimates (Ron and coll.) and a *pessimistic* evaluation of the thyroid doses. On this basis, the number of cases observed is *much greater than* that which would have been expected over 10 years, based on the experience of other populations exposed as children (based on Ron's Excess Relative Risks figures ; ERR=RR-1). This conclusion is the opposite of Goulko's and Jacob's one as regards the agreement with the results of previous studies.

In Cardis' study, no comparison was made on the basis of the excess absolute risk. According to Cardis, studies of other populations exposed in childhood to external irradiation indicate that such a model does not fit the observed data; moreover such a comparison may be inappropriate, since the length of follow-up period following the Chernobyl accident is much shorter than that of the other populations studied.

The use of ERR in Cardis' study was challenged, on account of the uncertainties regarding "baseline" cases ("spontaneous" cases), particularly in the first years of follow-up of young cohorts. However, as already mentioned earlier, choosing another country as baseline would affect the scale of the increase but not the relative age related sensitivity.

As regards Cardis' evaluation, the question was also raised whether Ron's (op. cit.) ERR estimate of 7.7 per Gy (persons exposed to radiation before age 15 years) is appropriate for the 0-5 years at exposure cohort, taking into account the possible specificity of their pattern of risk over time for radiation induced thyroid cancer.

> More conclusive information about the magnitude of the sensitivity of small children to radiation carcinogenesis in the thyroid could result from further studies *focalised on the 0-5 years at exposure cohort.* Those studies should more explicitly take into account the *temporal pattern* of the evolution of the epidemiological risk indicators (ERR and EAR), in the studies used for comparison.

Whatever the conclusion may be as regards this more or less pronounced sensitivity to radiation cancer induction in the youngest age at exposure cohort in Chernobyl and while the relative risk of exposure to external or internal irradiation cannot yet be quantified, it is clear that the low risk for *internal* radiation in adults must not be extrapolated to children, and particularly to young children, where there is clearly a significant risk of

developing thyroid cancer after exposure to radioiodines . The Chernobyl observations have also *confirmed* the enhanced sensitivity of children (of all ages) to radiation-induced thyroid cancer. It must be remembered in this respect that previously published data on external exposures had already given indication of a higher (lifetime) risk in the 0-15 years at exposure cohort of children (~1.5 % per Gy, according to NCRP, i .e. a factor 2 higher in comparison with the global ICRP figure and a factor ~3 higher in comparison with the NCRP adult's figures) and of an even higher risk in the 0-5 years at exposure cohort (factor 3 in the EAR for the 0-4 cohort with respect to the 5-15 cohort , according to the Israeli study reported by BEIR V, and factor 5 in the ERR for the 0-4 cohort with respect to the 10-14 cohort in Ron's pooled study).

The Chernobyl observations have also, if not confirmed, at least obviously demonstrated the *short latency* period of the radiation-induced childhood thyroid cancers, and, as well documented by **Pinchera**, the *aggressiveness* of these cancers in small children and the difficulties, complications and *long-lasting consequences* of the treatments.

3.2. Adult risk

With regard to the adult risk of radiation-induced thyroid cancer, there is an increase in the incidence of thyroid cancer in the adult populations exposed during the Chernobyl accident. From the data available at the present time, the hypothesis of an artefact due to a better screening cannot be dismissed. The difficulties experienced in the past to demonstrate a statistically significant increase in the incidence of various types of individual cancers in the first years (or even decades) after irradiation must prevent the drawing of premature conclusions.

3.3. Autoimmune thyroiditis

The risk of radiation-induced autoimmune thyroiditis was discussed by Pinchera. The data presented demonstrated an increased incidence of humoral thyroid autoimmunity (anti-thyroid antibodies) in a cohort of exposed children aged 0-9 years at the time of the accident. At the present time it is only a biological finding but previous observations suggest caution, due to the probability of hypothyroidism appearing later.

3.4. Host susceptibility factors and role of diet

The study of the possible modifying factors is still underway in Belarus and Russia. Among these factors, two of them are particularly invoked as a plausible explanation for the apparent discrepancy between the Chernobyl observations and previous ones: genetic predisposition and iodine deficiency . The hypothesis of a racial factor has also been raised.

Evidence of a genetic predisposition to thyroid cancer is growing and it raises the hypothesis that there may be local aggregations of predisposed families. Ten families were identified in Belarus where two siblings are affected by thyroid cancer. Further study is underway.

Iodine deficiency seems to exist in some areas of Belarus, Ukraine and Russia. This could be an important modifying factor but there is no available literature at the present time on the joint effects of radiation and iodine deficiency in the induction of thyroid cancers in humans.

As there are many areas in the world with iodine deficiency and as it is practically impossible to detect genetic predisposition, the final results of the studies on these modifying factors cannot be waited upon before deciding prophylaxis measures in the framework of nuclear emergency plans.

4.   POTENTIAL IMPLICATIONS

4.1. Intervention levels for iodine prophylaxis

In Publication 63, the ICRP recommends a range of intervention levels (average averted equivalent dose to thyroid) of **500** (almost always justified) to **50** (minimum optimised value) mSv for administration of stable iodine in the case of a radiological emergency.

In the Safety Series No 109, the IAEA recommends on the same grounds a single generic intervention level (IL) of **100** mGy and specifies that it is applicable to all age groups.

The same generic IL is also recommended in the international BSS (Safety Series No 115), formally adopted by several international agencies.

At the European level, the Radiation Protection 87 Report recommends a range of generic IL of **some tens to a few hundreds** mSv, based on a risk of radiation-induced thyroid cancer (both fatal and non-fatal) of 7.5×10^{-3} per Sv to the thyroid (average all ages risk factor of ICRP) and a risk range of side effects from the intake of stable iodine of 10^{-3} to 10^{-4} . The report recognizes (p. 26) that it leads to an optimized IL value of only **a few mSv** for infants.

In its Manual on public health action in radiation emergencies (1994), the European Centre for environment and Health of the WHO recommends that doses to the thyroid from radioactive isotopes of iodine, especially in children, should be kept **ALARA**, with a **10 mSv** dose as the lowest potential dose « at which intervention is practical ».

As the available epidemiological data are well fitted by a *linear* dose-response function, as the costs of the (prior or not) distribution of stable iodine are relatively trivial and as the risks of the administration of stable iodine to children are equally trivial, provided that medical follow-up of thyroid function is undertaken in the case of fœtuses and newborns, the major potential consequence of the Chernobyl observations may be the recommendation of **age-specific intervention levels,** which could be as low as 10 mSv (averted equivalent dose at the thyroid) for children (0-15 years) and in the order of 50-100 mSv for the young adults (up to 40 years).

With such IL for children, potential intervention areas will extend to several tens of kilometers, which implies specific provisions for the availability of stable iodine to children.

Nevertheless the introduction of a ban on consumption of fresh milk produced in that area will be an effective countermeasure.

As the risk of the administration of stable iodine to older adults depends on the existence and the degree of iodine deficiency in the affected area and on the efficacy of the preventive screening of the contra-indications and since the risk of radiation-induced thyroid cancer at these ages, although presumably low, cannot be dismissed at the present

time, there are no new grounds to modify the old recommendations for this category : IL should then lie in the range 100-500 mSv.

Some suggestions have been made for IL up to 5 Gy for adults over 40 years. However, as radiation-induced cancer risk cannot be totally dismissed for adults over 40 years, and as there is some evidence of risk of radiation-induced autoimmune thyroiditis at doses far below 5 Gy (Japanese bomb survivors), such high IL are strongly challenged and are unacceptable for the members of the RIHSS WP.

4.2. Weighting factor for thyroid and limitation of thyroid dose

ICRP recommendations concerning the calculation of the effective dose include the choice of a set of w_T for various tissues where radiation-induced cancers can occur. In the context of general recommendations with a safety margin, ICRP decided to use the same w_T for both sexes and all ages. ICRP took some account of the radiation induced non fatal cancers.

As radioiodine contamination may be the dominant one, the respect of the effective dose limit of 1 mSv for members of the public (including children) is still warranted with a dose of 20 mSv to the thyroid, i.e. twice the lower WHO suggested intervention level for children. On the same grounds, the effective dose limit for apprentices and students (6 mSv) corresponds to 120 mSv at the thyroid, again more than the IAEA generic IL and than the suggested IL for young adults, while the maximum 50 mSv annual effective dose for exposed workers may correspond to 1 Sv at the thyroid (higher than any recommended IL).

After an effective dose of *1 mSv*, the lifetime risk of radiation-induced fatal cancer is *5 x 10^{-5} for an adult,* according to ICRP, which is considered as sufficiently low and acceptable, in the framework of the system of dose limitation for practices.

A corresponding equivalent dose of *20 mSv at the thyroid <u>in children</u>* implies a lifetime risk of radiation-induced thyroid cancer (fatal or not) of 3×10^{-4} , according again to ICRP, which recommends the NCRP figures. As the recent evaluation of EAR (Ron's figures) is a factor 2 higher than the value used by NCRP (4.4 v/ 2×10^{-4} PY Gy $^{-1}$) and as the risk may be another factor 3 higher for the 0-5 year sub-group, as suggested by the Chernobyl observations and the Israeli studies, the present best estimate of the lifetime risk of radiation-induced thyroid cancer (fatal or not) after exposure of small children at a dose of 20 mSv at the thyroid *could be in the order of 10^{-3} .*

The underlying basic question is whether it is justified that the common system of limitation of dose proposed for adults and children, may correspond in some cases to risks which are significantly different and not necessarily acceptable (a small risk of fatal cancer after a long latency v/ a high risk of curable cancer but after a short latency and with long-lasting consequences).

Two ways can be followed to solve this problem: on the one hand, one can propose a *specific set of w_T for children :* ICRP has not proposed a separate set of w_T values for children or for in utero exposure, although it is considering these issues at present ; on the other hand, there is the possibility to restrict the dose at the thyroid by *additional thyroid dose constraint(s)* (in equivalent dose) for children (and possibly for students and apprentices and even for exposed workers). This should be the case in situations where the thyroid dose might be the outstanding one and might approach the value of the lower

intervention levels. It is a question for future recommendations as to whether effective dose is to be used in intervention and other situations involving significant doses to the thyroid.

4.3. Maximum permitted levels of radioactive iodine contamination of foodstuffs

According to the Council Regulation (Euratom) No 2218/89, maximum permitted levels of radioactive iodine contamination of foodstuffs are established for future radiological emergencies. Consumption of one liter of milk by a 1 year old child at the maximum radioiodine (^{131}I) concentration of 500 Bq/l corresponds to a thyroid dose of 1.8 mSv, on the basis of the ingestion dose coefficient of 3.6 E -06 Sv/Bq . The WHO IL for thyroid dose of 10 mSv will be reached after drinking 5 to 6 liters of that milk .

As there will be some temptation for milk producers, after a nuclear accident, to consider the 500 Bq/kg as a safe figure, such that dairy produces are put on the market systematically after radioiodine has decreased at this maximum permitted level, children could be exposed over a prolonged period and so accumulate higher thyroid doses than those which would be considered as an IL for exposure through the inhalation pathway.

In the absence of a revision of the figures in the regulation, which could probably reopen old discussions, a possible solution should be searched through a regulatory provision (or at least through a recommendation) decreasing the maximum radioiodine permitted concentrations with time after the accident.

ABSTRACT

One of the major health consequences of the accident at the Chernobyl power station in April 1986 is the sudden and great increase in the number of persons, particularly children, with thyroid carcinoma.

The presentations made at the seminar reviewed the existing knowledge on the subject of radiation induced thyroid diseases especially in relation to the Chernobyl accident.

The subject was treated from the four points of view

➢ Genetic and environmental factors influencing the radiation induced cancer risk

➢ Thyroid doses reconstruction and risk after the Chernobyl accident

➢ Age and molecular biology

➢ Lessons learned following the Chernobyl accident

The publication is completed by considerations on the conclusions that can be drawn from the seminar and on the potential implications of the informations presented on the development of the European Union radiation protection legislation.

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