
Guidance

Potassium Iodide as a Thyroid Blocking Agent in Radiation Emergencies

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I. INTRODUCTION

The objective of this document is to provide guidance to other Federal agencies, including the Environmental Protection Agency (EPA) and the Nuclear Regulatory Commission (NRC), and to state and local governments regarding the safe and effective use of potassium iodide (KI) as an adjunct to other public health protective measures in the event that radioactive iodine is released into the environment. The adoption and implementation of these recommendations are at the discretion of the state and local governments responsible for developing regional emergency-response plans related to radiation emergencies.

This guidance updates the Food and Drug Administration (FDA) 1982 recommendations for the use of KI to reduce the risk of thyroid cancer in radiation emergencies involving the release of radioactive iodine. The recommendations in this guidance address KI dosage and the projected radiation exposure at which the drug should be used.

These recommendations were prepared by the Potassium Iodide Working Group, comprising scientists from the FDA's Center for Drug Evaluation and Research (CDER) and Center for Devices and Radiological Health (CDRH) in collaboration with experts in the field from the National Institutes of Health (NIH). Although they differ in two respects (as discussed in Section IV.B), these revised recommendations are in general accordance with those of the World Health Organization (WHO), as expressed in its *Guidelines for Iodine Prophylaxis Following Nuclear Accidents: Update 1999* (WHO 1999).

II. BACKGROUND

Under 44 CFR 351, the Federal Emergency Management Agency (FEMA) has established roles and responsibilities for Federal agencies in assisting state and local governments in their radiological emergency planning and preparedness activities. The Federal agencies, including the Department of Health and Human Services (HHS), are to carry out these roles and responsibilities as members of the Federal Radiological Preparedness Coordinating Committee

(FRPCC). Under 44 CFR 351.23(f), HHS is directed to provide guidance to state and local governments on the use of radioprotective substances and the prophylactic use of drugs (e.g., KI) to reduce the radiation dose to specific organs. This guidance includes information about dosage and projected radiation exposures at which such drugs should be used.

The FDA has provided guidance previously on the use of KI as a thyroid blocking agent. In the *Federal Register* of December 15, 1978, FDA announced its conclusion that KI is a safe and effective means by which to block uptake of radioiodines by the thyroid gland in a radiation emergency under certain specified conditions of use. In the *Federal Register* of June 29, 1982, FDA announced final recommendations on the administration of KI to the general public in a radiation emergency. Those recommendations were formulated after reviewing studies relating radiation dose to thyroid disease risk that relied on estimates of *external* thyroid irradiation after the nuclear detonations at Hiroshima and Nagasaki and analogous studies among children who received therapeutic radiation to the head and neck. Those recommendations concluded that at a projected dose to the thyroid gland of 25 cGy or greater from ingested or inhaled radioiodines, the risks of short-term use of small quantities of KI were outweighed by the benefits of suppressing radioiodine-induced thyroid cancer.¹ The amount of KI recommended at that time was 130 mg per day for adults and children above 1 year of age and 65 mg per day for children below 1 year of age. The guidance that follows revises our 1982 recommendations on the use of KI for thyroid cancer prophylaxis based on a comprehensive review of the data relating radioiodine exposure to thyroid cancer risk accumulated in the aftermath of the 1986 Chernobyl reactor accident.

III. DATA SOURCES

A. Reliance on Data from Chernobyl

In epidemiological studies investigating the relationship between thyroidal radioiodine exposure and risk of thyroid cancer, the estimation of thyroid radiation doses is a critical and complex aspect of the analyses. Estimates of exposure, both for individuals and across populations, have been reached in different studies by the variable combination of (1) direct thyroid measurements in a segment of the exposed population; (2) measurements of ¹³¹I (iodine isotope) concentrations in the milk consumed by different groups (e.g., communities) and of the quantity of milk consumed; (3) inference from ground deposition of long-lived radioisotopes released coincidentally and presumably in fixed ratios with radioiodines; and (4) reconstruction of the nature and extent of the actual radiation release.

All estimates of individual and population exposure contain some degree of uncertainty. The uncertainty is least for estimates of individual exposure based on direct thyroid measurements.

¹ For the radiation emitted by ¹³¹I (electrons and photons), the radiation-weighting factor is equal to one, so that the absorbed dose to the thyroid gland expressed in centigrays (cGy) is numerically equal to the thyroid equivalent dose expressed in rem (1 cGy = 1 rem).

Uncertainty increases with reliance on milk consumption estimates; is still greater with estimates derived from ground deposition of long-lived radioisotopes, and is highest for estimates that rely heavily on release reconstruction.

Direct measurements of thyroid radioactivity are unavailable from the Hanford, Nevada Test Site, and Marshall Islands exposures. Indeed, the estimates of thyroid radiation doses related to these releases rely heavily on release reconstructions and, in the former two cases, on recall of the extent of milk consumption 40 to 50 years after the fact. In the Marshall Islands cohort, urinary radioiodine excretion data were obtained and used in calculating exposure estimates.

Because of the great uncertainty in the dose estimates from the Hanford and Nevada Test Site exposures and due to the small numbers of thyroid cancers occurring in the populations potentially exposed, the epidemiological studies of the excess thyroid cancer risk related to these radioiodine releases are, at best, inconclusive. As explained below, the dosimetric data derived in the studies of individual and population exposures following the Chernobyl accident, although not perfect, are unquestionably superior to data from previous releases. In addition, the results of the earlier studies are inadequate to refute cogent case control study evidence from Chernobyl of a cause-effect relationship between thyroid radioiodine deposition and thyroid cancer risk.²

The Chernobyl reactor accident of April 1986 provides the best-documented example of a massive radionuclide release in which large numbers of people across a broad geographical area were exposed acutely to radioiodines released into the atmosphere. Therefore, the recommendations contained in this guidance are derived from our review of the Chernobyl data as they pertain to the large number of thyroid cancers that occurred. These are the most comprehensive and reliable data available describing the relationship between thyroid radiation dose and risk for thyroid cancer following an environmental release of ¹³¹I. In contrast, the exposures resulting from radiation releases at the Hanford Site in Washington State in the mid-1940s and in association with the nuclear detonations at the Nevada Test Site in the 1950s were extended over years, rather than days to weeks, contributing to the difficulty in estimating radioactive dose in those potentially exposed (Davis et al., 1999; Gilbert et al., 1998). The exposure of Marshall Islanders to fallout from the nuclear detonation on Bikini in 1954 involved relatively few people, and although the high rate of subsequent thyroid nodules and cancers in the exposed population was likely caused in large part by radioiodines, the Marshall Islands data provide little insight into the dose-response relationship between radioactive iodine exposure and thyroid cancer risk (Robbins and Adams 1989).

Beginning within a week after the Chernobyl accident, direct measurements of thyroid exposure were made in hundreds of thousands of individuals, across three republics of the former Soviet Union (Robbins and Schneider 2000, Gavrilin et al., 1999, Likhtarev et al., 1993, Zvonova and Balonov 1993). These thyroid measurements were used to derive, in a direct manner, the thyroid doses received by the individuals from whom the measurements were taken. The thyroid measurements were also used as a guide to estimate the thyroid doses received by other people, taking into account differences in age, milk consumption rates, and ground deposition densities, among other things. The thyroid doses derived from thyroid measurements have a large degree

² We have included in this guidance an extensive bibliography of the sources used in developing these revised recommendations.

of uncertainty, especially in Belarus, where most of the measurements were made by inexperienced people with detectors that were not ideally suited to the task at hand (Gavrilin et al., 1999 and UNSCEAR 2000). However, as indicated above, the uncertainties attached to thyroid dose estimates derived from thyroid measurements are, as a rule, lower than those obtained without recourse to those measurements.

It is also notable that the thyroid radiation exposures after Chernobyl were virtually all *internal*, from radioiodines. Despite some degree of uncertainty in the doses received, it is reasonable to conclude that the contribution of external radiation was negligible for most individuals. This distinguishes the Chernobyl exposures from those of the Marshall Islanders. Thus, the increase in thyroid cancer seen after Chernobyl is attributable to ingested or inhaled radioiodines. A comparable burden of excess thyroid cancers could conceivably accrue should U.S. populations be similarly exposed in the event of a nuclear accident. This potential hazard highlights the value of averting such risk by using KI as an adjunct to evacuation, sheltering, and control of contaminated foodstuffs.

B. Thyroid Cancers in the Aftermath of Chernobyl

The Chernobyl reactor accident resulted in massive releases of ^{131}I and other radioiodines. Beginning approximately 4 years after the accident, a sharp increase in the incidence of thyroid cancer among children and adolescents in Belarus and Ukraine (areas covered by the radioactive plume) was observed. In some regions, for the first 4 years of this striking increase, observed cases of thyroid cancer among children aged 0 through 4 years at the time of the accident exceeded expected number of cases by 30- to 60-fold. During the ensuing years, in the most heavily affected areas, incidence is as much as 100-fold compared to pre-Chernobyl rates (Robbins and Schneider 2000; Gavrilin et al., 1999; Likhtarev et al., 1993; Zvonova and Balonov 1993). The majority of cases occurred in children who apparently received less than 30 cGy to the thyroid (Astakhova et al., 1998). A few cases occurred in children exposed to estimated doses of < 1 cGy; however, the uncertainty of these estimates confounded by medical radiation exposures leaves doubt as to the causal role of these doses of radioiodine (Souchkevitch and Tsyb 1996).

The evidence, though indirect, that the increased incidence of thyroid cancer observed among persons exposed during childhood in the most heavily contaminated regions in Belarus, Ukraine, and the Russian Federation is related to exposure to iodine isotopes is, nevertheless, very strong (IARC 2001). We have concluded that the best dose-response information from Chernobyl shows a marked increase in risk of thyroid cancer in children with exposures of 5 cGy or greater (Astakhova et al., 1998; Ivanov et al., 1999; Kazakov et al., 1992). Among children born more than nine months after the accident in areas traversed by the radioactive plume, the incidence of thyroid cancer has not exceeded preaccident rates, consistent with the short half-life of ^{131}I .

The use of KI in Poland after the Chernobyl accident provides us with useful information regarding its safety and tolerability in the general population. Approximately 10.5 million children under age 16 and 7 million adults received at least one dose of KI. Of note, among newborns receiving single doses of 15 mg KI, 0.37 percent (12 of 3214) showed transient increases in TSH (thyroid stimulating hormone) and decreases in FT4 (free thyroxine). The side

effects among adults and children were generally mild and not clinically significant. Side effects included gastrointestinal distress, which was reported more frequently in children (up to 2 percent, felt to be due to bad taste of SSKI solution) and rash (~1 percent in children and adults). Two allergic reactions were observed in adults with known iodine sensitivity (Nauman and Wolff 1993).

Thus, the studies following the Chernobyl accident support the etiologic role of relatively small doses of radioiodine in the dramatic increase in thyroid cancer among exposed children. Furthermore, it appears that the increased risk occurs with a relatively short latency. Finally, the Polish experience supports the use of KI as a safe and effective means by which to protect against thyroid cancer caused by internal thyroid irradiation from inhalation of contaminated air or ingestion of contaminated food and drink when exposure cannot be prevented by evacuation, sheltering, or food and milk control.

IV. CONCLUSIONS AND RECOMMENDATIONS

A. Use of KI in Radiation Emergencies: Rationale, Effectiveness, Safety

For the reasons discussed above, the Chernobyl data provide the most reliable information available to date on the relationship between internal thyroid radioactive dose and cancer risk. They suggest that the risk of thyroid cancer is inversely related to age, and that, especially in young children, it may accrue at very low levels of radioiodine exposure. We have relied on the Chernobyl data to formulate our specific recommendations below.

The effectiveness of KI as a specific blocker of thyroid radioiodine uptake is well established (Il' in LA, et al., 1972) as are the doses necessary for blocking uptake. As such, it is reasonable to conclude that KI will likewise be effective in reducing the risk of thyroid cancer in individuals or populations at risk for inhalation or ingestion of radioiodines.

Short-term administration of KI at thyroid blocking doses is safe and, in general, more so in children than adults. The risks of stable iodine administration include sialadenitis (an inflammation of the salivary gland, of which no cases were reported in Poland among users after the Chernobyl accident), gastrointestinal disturbances, allergic reactions and minor rashes. In addition, persons with known iodine sensitivity should avoid KI, as should individuals with dermatitis herpetiformis and hypocomplementemic vasculitis, extremely rare conditions associated with an increased risk of iodine hypersensitivity.

Thyroidal side effects of stable iodine include iodine-induced thyrotoxicosis, which is more common in older people and in iodine deficient areas but usually requires repeated doses of stable iodine. In addition, iodide goiter and hypothyroidism are potential side effects more common in iodine sufficient areas, but they require chronic high doses of stable iodine (Rubery 1990). In light of the preceding, individuals with multinodular goiter, Graves' disease, and autoimmune thyroiditis should be treated with caution, especially if dosing extends beyond a few days. The vast majority of such individuals will be adults.

The transient hypothyroidism observed in 0.37 percent (12 of 3214) of neonates treated with KI in Poland after Chernobyl has been without reported sequelae to date. There is no question that the benefits of KI treatment to reduce the risk of thyroid cancer outweigh the risks of such treatment in neonates. Nevertheless, in light of the potential consequences of even transient hypothyroidism for intellectual development, we recommend that neonates (within the first month of life) treated with KI be monitored for this effect by measurement of TSH (and FT4, if indicated) and that thyroid hormone therapy be instituted in cases in which hypothyroidism develops (Bongers-Schokking 2000; Fisher 2000; Calaciura 1995).

B. KI Use in Radiation Emergencies: Treatment Recommendations

After careful review of the data from Chernobyl relating estimated thyroid radiation dose and cancer risk in exposed children, FDA is revising its recommendation for administration of KI based on age, predicted thyroid exposure, and pregnancy and lactation status (see Table).

| Threshold Thyroid Radioactive Exposures and Recommended Doses of KI for Different Risk Groups | | | | |
|--|---------------------------------|--------------|---------------------|--------------------|
| | Predicted Thyroid exposure(cGy) | KI dose (mg) | # of 130 mg tablets | # of 65 mg tablets |
| Adults over 40 yrs | ≥ 500 | 130 | 1 | 2 |
| Adults over 18 through 40 yrs | ≥ 10 | | | |
| Pregnant or lactating women | ≥ 5 | | | |
| Adoles. over 12 through 18 yrs* | | 65 | 1/2 | 1 |
| Children over 3 through 12 yrs | | 32 | 1/4 | 1/2 |
| Over 1 month through 3 years | | 16 | 1/8 | 1/4 |
| Birth through 1 month | | | | |

*Adolescents approaching adult size (≥ 70 kg) should receive the full adult dose (130 mg).

The protective effect of KI lasts approximately 24 hours. For optimal prophylaxis, KI should therefore be dosed daily, until a risk of significant exposure to radioiodines by either inhalation or ingestion no longer exists. Individuals intolerant of KI at protective doses, and neonates, pregnant and lactating women (in whom repeat administration of KI raises particular safety issues, see below) should be given priority with regard to other protective measures (i.e., sheltering, evacuation, and control of the food supply).

Note that adults over 40 need take KI only in the case of a projected large internal radiation dose to the thyroid (>500 cGy) to prevent hypothyroidism.

These recommendations are meant to provide states and local authorities as well as other agencies with the best current guidance on safe and effective use of KI to reduce thyroidal radioiodine exposure and thus the risk of thyroid cancer. FDA recognizes that, in the event of an emergency, some or all of the specific dosing recommendations may be very difficult to carry

out given their complexity and the logistics of implementation of a program of KI distribution. The recommendations should therefore be interpreted with flexibility as necessary to allow optimally effective and safe dosing given the exigencies of any particular emergency situation. In this context, we offer the following critical general guidance: ***across populations at risk for radioiodine exposure, the overall benefits of KI far exceed the risks of overdosing, especially in children, though we continue to emphasize particular attention to dose in infants.***

These FDA recommendations differ from those put forward in the World Health Organization (WHO) 1999 guidelines for iodine prophylaxis in two ways. WHO recommends a 130-mg dose of KI for adults and adolescents (over 12 years). For the sake of logistical simplicity in the dispensing and administration of KI to children, FDA recommends a 65-mg dose as standard for all school-age children while allowing for the adult dose (130 mg, 2 X 65 mg tablets) in adolescents approaching adult size. The other difference lies in the threshold for predicted exposure of those up to 18 years of age and of pregnant or lactating women that should trigger KI prophylaxis. WHO recommends a threshold of 1 cGy for these two groups. As stated earlier, FDA has concluded from the Chernobyl data that the most reliable evidence supports a significant increase in the risk of childhood thyroid cancer at exposures of 5 cGy or greater.

The downward KI dose adjustment by age group, based on body size considerations, adheres to the principle of minimum effective dose. The recommended standard dose of KI for all school-age children is the same (65 mg). However, adolescents approaching adult size (i.e., >70 kg) should receive the full adult dose (130 mg) for maximal block of thyroid radioiodine uptake. Neonates ideally should receive the lowest dose (16 mg) of KI. Repeat dosing of KI should be avoided in the neonate to minimize the risk of hypothyroidism during that critical phase of brain development (Bongers-Schokking 2000; Calaciura et al., 1995). KI from tablets (either whole or fractions) or as fresh saturated KI solution may be diluted in milk, formula, or water and the appropriate volume administered to babies. As stated above, we recommend that neonates (within the first month of life) treated with KI be monitored for the potential development of hypothyroidism by measurement of TSH (and FT4, if indicated) and that thyroid hormone therapy be instituted in cases in which hypothyroidism develops (Bongers-Schokking 2000; Fisher 2000; Calaciura et al., 1995).

Pregnant women should be given KI for their own protection and for that of the fetus, as iodine (whether stable or radioactive) readily crosses the placenta. However, because of the risk of blocking fetal thyroid function with excess stable iodine, repeat dosing with KI of pregnant women should be avoided. Lactating females should be administered KI for their own protection, as for other young adults, and potentially to reduce the radioiodine content of the breast milk, but not as a means to deliver KI to infants, who should get their KI directly. As for direct administration of KI, stable iodine as a component of breast milk may also pose a risk of hypothyroidism in nursing neonates. Therefore, repeat dosing with KI should be avoided in the lactating mother, except during continuing severe contamination. If repeat dosing of the mother is necessary, the nursing neonate should be monitored as recommended above.

V. ADDITIONAL CONSIDERATIONS IN PROPHYLAXIS AGAINST THYROID RADIOIODINE EXPOSURE

Certain principles should guide emergency planning and implementation of KI prophylaxis in the event of a radiation emergency. After the Chernobyl accident, across the affected populations, thyroid radiation exposures occurred largely due to consumption of contaminated fresh cow's milk (this contamination was the result of milk cows grazing on fields affected by radioactive fallout) and to a much lesser extent by consumption of contaminated vegetables. In this or similar accidents, for those residing in the immediate area of the accident or otherwise directly exposed to the radioactive plume, inhalation of radioiodines may be a significant contributor to individual and population exposures. As a practical matter, it may not be possible to assess the risk of thyroid exposure from inhaled radioiodines at the time of the emergency. The risk depends on factors such as the magnitude and rate of the radioiodine release, wind direction and other atmospheric conditions, and thus may affect people both near to and far from the accident site.

For optimal protection against inhaled radioiodines, KI should be administered before or immediately coincident with passage of the radioactive cloud, though KI may still have a substantial protective effect even if taken 3 or 4 hours after exposure. Furthermore, if the release of radioiodines into the atmosphere is protracted, then, of course, even delayed administration may reap benefits by reducing, if incompletely, the total radiation dose to the thyroid.

Prevention of thyroid uptake of ingested radioiodines, once the plume has passed and radiation protection measures (including KI) are in place, is best accomplished by food control measures and not by repeated administration of KI. Because of radioactive decay, grain products and canned milk or vegetables from sources affected by radioactive fallout, if stored for weeks to months after production, pose no radiation risk. Thus, late KI prophylaxis at the time of consumption is not required.

As time is of the essence in optimal prophylaxis with KI, timely administration to the public is a critical consideration in planning the emergency response to a radiation accident and requires a ready supply of KI. State and local governments choosing to incorporate KI into their emergency response plans may consider the option of predistribution of KI to those individuals who do not have a medical condition precluding its use.

VI. SUMMARY

FDA maintains that KI is a safe and effective means by which to prevent radioiodine uptake by the thyroid gland, under certain specified conditions of use, and thereby obviate the risk of thyroid cancer in the event of a radiation emergency. Based upon review of the literature, we have proposed lower radioactive exposure thresholds for KI prophylaxis as well as lower doses of KI for neonates, infants, and children than we recommended in 1982. As in our 1982 notice in the *Federal Register*, FDA continues to recommend that radiation emergency response plans include provisions, in the event of a radiation emergency, for informing the public about the magnitude of the radiation hazard, about the manner of use of KI and its potential benefits and

risks, and for medical contact, reporting, and assistance systems. FDA also emphasizes that emergency response plans and any systems for ensuring availability of KI to the public should recognize the critical importance of KI administration in advance of exposure to radioiodine. As in the past, FDA continues to work in an ongoing fashion with manufacturers of KI to ensure that high-quality, safe, and effective KI products are available for purchase by consumers as well as by state and local governments wishing to establish stores for emergency distribution.

KI provides protection only for the thyroid from radioiodines. It has no impact on the uptake by the body of other radioactive materials and provides no protection against external irradiation of any kind. FDA emphasizes that the use of KI should be as an adjunct to evacuation (itself not always feasible), sheltering, and control of foodstuffs.

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