世卫组织：人类营养中的维生素和矿物质需求（第二版）

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概述

在过去的 20 年中，微量营养素在公共卫生方面变得非常重要。因此，进行了大量的研究，以更好地了解其生理作用和微量营养素缺乏饮食的健康后果，建立定义微量营养素营养不良公共卫生严重程度的标准，并制定预防和控制策略。

这个过程的主要成果之一是对人类微量营养素需求有了极大的改善，这是理解微量营养素营养不良的公共卫生意义并确定预防措施的最重要步骤。这个过程还导致了联合国粮农组织（FAO）、世界卫生组织（WHO）和国际原子能机构（IAEA）共同进行的连续专家咨询和出版物，提供了最新的知识并定义了微量营养素需求的标准。

鉴于这一迅速发展的领域，以及自 1996 年最近一次出版物以来所取得的重大新进展，粮农组织和世界卫生组织认为有必要召开新的专家咨询会，重新评估微量营养素在人类健康和营养中的作用。这于 1998 年 9 月举行。

这本书展示了咨询的成果，并结合了之后获得的最新证据，以回答在咨询时基于当时最佳科学信息仍不明确或有争议的一些问题。

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16. 碘

16.1 碘在人体代谢过程中的作用

目前，碘在人体内已知的唯一生理作用是甲状腺合成甲状腺激素。因此，碘的膳食需求量是由甲状腺正常产生甲状腺素 （T4） 来确定的，而不会强调甲状腺碘捕获机制或提高促甲状腺激素 （TSH） 水平。

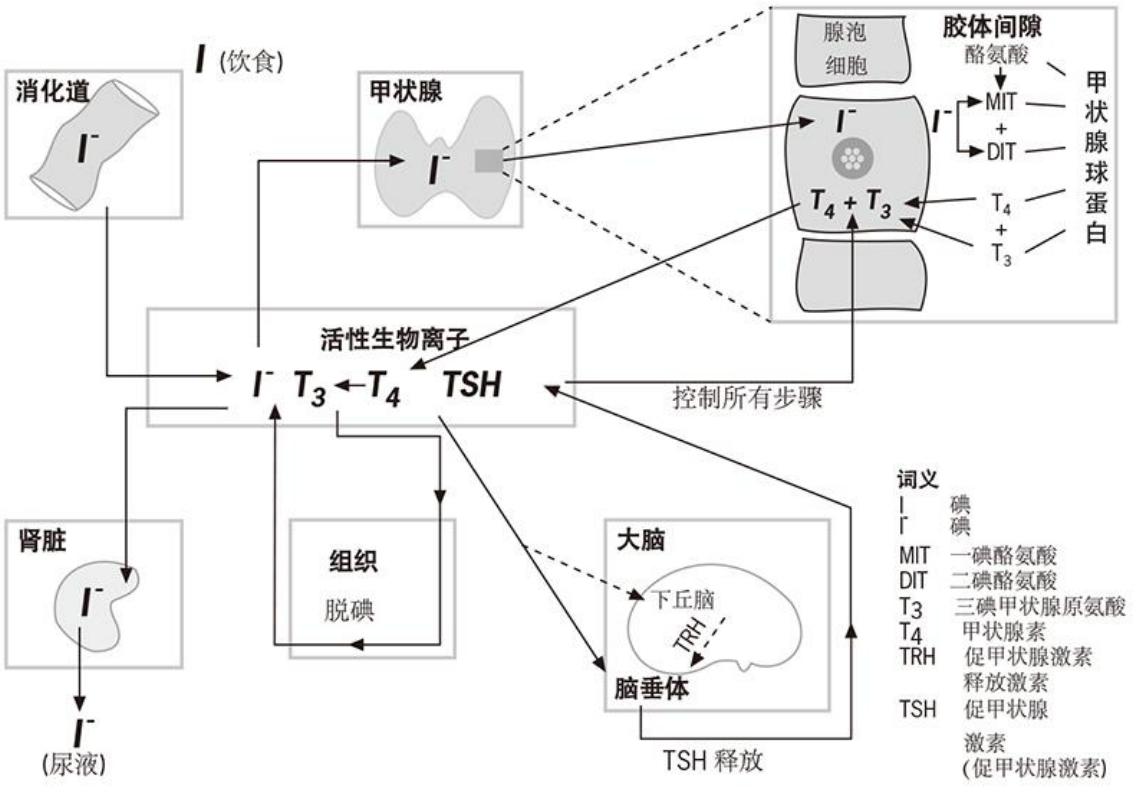
饮食中的碘被整个胃肠道吸收。膳食碘在被吸收之前会转化为碘离子。碘离子具有 100% 的生物利用度，完全从食物和水中吸收。然而，对于为治疗目的而摄入的甲状腺激素中的碘来说，情况并非如此。

碘以血浆无机碘的形式进入循环，由甲状腺和肾脏从循环中清除。碘被甲状腺用于合成甲状腺激素，肾脏随尿液排泄过量的碘。尿液中碘的排泄是碘摄入量的良好衡量标准。在正常人群中，没有地方性甲状腺肿或地方性克汀病形式的临床碘缺乏症证据，尿碘排泄反映了平均每日碘需求量。因此，为了确定碘需求量和碘摄入量，重要的指标是血清 T4 和 TSH 水平（探索甲状腺状态）和尿碘排泄量（探索碘摄入量）。图 16.1 给出了碘代谢回路的简化图。

碘的所有生物作用都归因于甲状腺激素。甲状腺分泌的主要甲状腺激素是 T4。循环中的 T4 被细胞吸收，并被细胞质中的 5¢-单脱碘酶脱碘，将其转化为三碘甲状腺原氨酸 （T3），这是甲状腺激素的活性形式。T3 遍

历细胞核并与核接收器结合。T3 的所有生物作用都是通过与核受体结合介导的，核受体控制特定基因的转录以实现特定蛋白质的合成。

图 16.1 甲状腺激素产生和调节总结



来源： 参考 （1）

甲状腺激素的生理作用可分为1）生长发育和2）控制体内代谢过程。甲状腺激素在人类从妊娠 15 周到 3 岁的大脑和中枢神经系统的生长发育中起着重要作用。如果在此期间存在碘缺乏症并导致甲状腺激素缺乏症，其后果是大脑和中枢神经系统发育紊乱。这些混乱是不可逆转的;最严重的形式是克汀病。表 16.1 给出了碘缺乏对生命不同阶段的影响。甲状腺激素的另一个生理作用是控制体内的几个代谢过程。这些包括碳水化合物、脂肪、蛋白质、维生素和矿物质代谢。例如，甲状腺激素增加能量产生，增加脂肪分解，并调节新糖生成和糖酵解。

16.2 有碘缺乏风险的人群

碘缺乏症影响到生命各个阶段的所有人群，从宫内阶段到老年，如表16.1 所示。但是，孕妇、哺乳期妇女、育龄妇女和 3 岁以下的儿童被认为是诊断和治疗碘缺乏症的最重要群体 （2， 5），因为在胎儿和新生儿生长发育过程中发生的碘缺乏会导致大脑和中枢神经系统的不可逆损伤，从而导致不可逆的智力低下。

表 16.1 碘缺乏症的影响，按生命阶段划分

人生阶段	影响
胎儿	流产 死产 先天性异常 围产期死亡率增加 婴儿死亡率增加 神经性克汀病：智力缺陷、耳聋缄默症、痉挛性双瘫和斜视 粘液性水肿性 克汀病：智力缺陷、甲状腺功能减退症和侏儒症 精神运动缺陷
新生儿	新生儿甲状腺肿 新生儿甲状腺功能减退症
儿童和青少年	甲状腺肿 青少年甲状腺功能减退症 精神功能受损 身体发育迟缓
成人	甲状腺肿及其并发症 甲状腺功能减退症 精神功能受损 碘诱发的甲状腺功能亢进症

来源：改编自参考文献 （2-4）。

16.3 碘的膳食来源

食物的碘含量取决于生长它的土壤的碘含量。存在于地壳上部的碘被冰川作用和反复的洪水浸出，并被带到大海中。因此，海水是碘的丰富来源 （6）。位于珊瑚礁附近的海藻具有从海洋中浓缩碘的固有生物能力。

以海藻为生的珊瑚鱼也富含碘。因此，食用海藻和珊瑚鱼的人群将摄入大量碘，就像日本的情况一样。日本人的碘摄入量通常在 2-3 mg/day 毫克/天的范围内 (6)。在非洲、亚洲、拉丁美洲和欧洲部分地区的几个地区，碘摄入量从 20 到 80 μg/day 不等。在加拿大和美国以及欧洲的一些地区，摄入量约为 500 μg/day 。平均碘含量表 16.2 给出了 Koμtras 等人 (6) 报告的食物（新鲜和干基）。

表 16.2 食物的平均碘含量 （μg/kg）

食物	新鲜		干基	
	平均值	范围	平均值	范围
鱼（淡水）	30	17 – 40	116	68 – 194
鱼（海洋）	832	163 – 3180	3715	471 – 4591
贝类	798	308 – 1300	3866	1292 – 4987
肉类	50	27 – 97	—	—
牛奶	47	35 – 56	—	—
鸡蛋	93	—	—	—
谷物	47	22 – 72	65	34 – 92
水果	18	10–29	154	62–27
豆类	30	23 – 36	234	223 – 245
蔬菜	29	12 – 201	385	204 – 1636

来源： 参考 (6)

表 16.3 选定环境介质的碘含量

中等	碘含量
陆地空气	1 μg/l
海洋空气	100 μg/l
陆地水	5 μg/l
海水	50 μg/l
火成岩	500 μg/kg
火成岩土壤	9000 μg/kg
沉积岩	1500 μg/kg
沉积岩土壤	4000 μg/kg
变质岩	1600 μg/kg
变质岩土壤	5000 μg/kg

来源： 参考 (6)

食物中的碘含量随地理位置而变化，因为各种环境介质的碘含量差异很大（表 16.3）(6)。因此，表 16.2 所示食物的平均碘含量不能普遍用于估计碘摄入量。

16.4 碘的推荐摄入量

美国国家科学院食品和营养委员会于 1989 年推荐的碘摄入量为婴儿（0-6 个月）每天 40 μg/day，大一些的婴儿（7-12 个月）每天 50μg/day ，儿童(1-10 岁)60-100 μg/day,青少年和 成人 150 μg/day（7)。这些值约为 0-12 个月婴儿 7.5 μg/kg/day，1-10 岁儿童 5.4 μg/kg/day，青少年和成人 2 μg/kg/day。提出这些量是为了允许正常的 T4 产生，而不会强调甲状腺碘捕获机制或提高 TSH 水平。

16.4.1 婴儿

推荐 0-6 个月大的婴儿每天摄入 40 μg/day（或 8 μg/kg/day、7mg/100 kcal 或 50 μg/l 牛奶）可能基于 1960 年代后期报道的观察结果，即母乳中的碘含量约为 50 μg/day，并假设以令人满意的速度生长的母乳喂养婴儿的营养代表了足够的营养摄入水平（8， 9)。然而，最近的数据表明,母乳中的碘含量随着人口碘摄入量的函数而显着变化 (10)。例如,欧洲的浓度范围为 20 至 330 μg/l,美国的浓度范围为 30 至 490 μg/l （8，10，11)。在严重缺碘的人群中,它低至 12 μg/l （8，10)。在此基础上，平均每天摄入 750 ml/day 母乳，欧洲的碘摄入量约为 60 μg/day，在美国约为 120 μg/day。美国上限值 （490μg/l） 将为一个 5 公斤的婴儿提供 368 μg/kg/da 或 68 μg/kg/day。

为了增加婴儿甲状腺的碘储存量，婴儿期需要保持碘的正平衡，只有

当足月婴儿的碘摄入量至少为 15 μg/kg/day，早产婴儿的碘摄入量至少为 30μg/kg/day 时，才能实现这一平衡（1）。早产婴儿的碘需求量是足月婴儿的两倍，因为早产婴儿对碘的保留率要低得多（8, 12。假设一个 6 个月大的孩子的平均体重为 6 kg，那么 15 μg/kg/day 大约相当于每天 90 μg/day 毫克的碘摄入量和需求。这个值是目前美国推荐量的两倍。

基于这些考虑，世界卫生组织 （WHO） 于 2001 年更新了其 1996 年的建议（13），并与联合国儿童基金会（MNICEF）和国家控制碘缺乏病委员会（ICCIDD） 一起提议，从出生开始碘摄入量为 90 μg/day （14）。为达到这个目标，在每天约 150 ml/kg/day 奶的摄入量基础上，进一步建议将配方奶的碘含量由前者建议的 50μg/l 增加至足月婴儿的 100μg/l，以及早产儿的碘含量至 200μg/l。

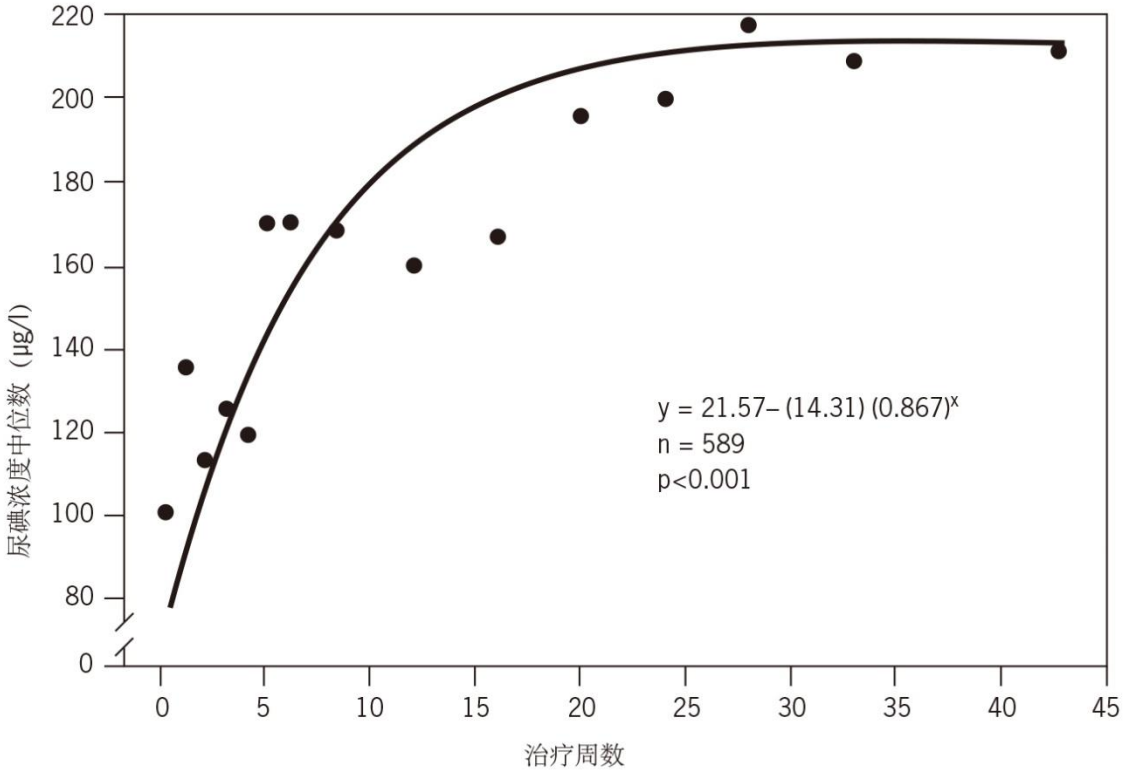
对于约 4-6 dl/day 的尿量，表明碘补充的尿碘浓度应在 150-220 μg/l 的范围内(1.18－1.73 μmol/l）在 0-3 岁的婴儿中。在欧洲 （15）、加拿大 （16） 和美国 （16） 的碘充足婴儿中观察到了这样的值。在中度碘缺乏的情况下，例如在比利时，这个年龄组的平均尿碘浓度仅为 100 μg/l （0.80 μmol/l）。只有在每天补充碘的第 30 周，生理剂量为 90 μg/day（17， 18），它才达到约 200 μg/l （1.57 μmol/l）的稳定正常值 （图 16.2）。

当新生儿和婴儿的尿碘浓度低于 50-60 μg/l（0.39-0.47 μmol/l）的阈值时，相当于摄入 25-35 μg/day，新生儿血清 TSH 值的患病率突然增加，超过 50 mM/ml，表明亚临床甲状腺功能减退症，最终并发为短暂性新生儿甲状腺功能减退症 （19）。当尿碘浓度在 10-20 μg/l （0.08

– 0.16 μmol/l）范围内时，如在严重地方性甲状腺肿的人群中观察到的那样，高达 10% 的新生儿患有明显的严重甲状腺功能减退症，血清 TSH 水平高于 100 μg/l，血清 T4 值低于 30 μg/l（39 μmol/l）（19）。如果不及时治疗，这些婴儿会发展为粘液性水肿性地方性克汀病 （20）。

图 16.2

6-36 个月大的比利时健康婴儿尿中位碘浓度随时间的变化，补充碘为 90 μg/kg/day，持续 44 周（每个点代表 32-176 次碘测定）



来源：参考文献 （18）。

总体而言，现有数据表明，小婴儿的碘需求量为 15 μg/kg/day（早产儿为 30 μg/kg/day）。当碘摄入量约为该值的三分之一时，就会发生高促甲状腺素血症（血清 TSH 水平高），表明亚临床甲状腺功能减退症有脑损伤的风险，而当摄入量约为该值的十分之一时，就会发生戏剧性的新

生儿甲状腺功能减退症，导致地方性克汀病。

16.4.2 儿童

按体重计算的每日碘需求量随着年龄的增长而逐渐减少。Tovar 及其同事 （21） 的一项研究将墨西哥农村 9-13 岁学童的 24 小时甲状腺放射性碘摄取与尿碘排泄相关联,结果表明,碘摄入量超过 60 μg/day 与 24 小时甲状腺放射性碘摄入量低于 30% 有关。较低的排泄值与较高的摄取值相关。碘摄入量为 60 μg/day 相当于平均体型 3 岁儿童(体重约为 20 公斤)的 3 μg/kg/day。因此,对于 1-10 岁的儿童来说,每天摄入 60-100 μg/day 似乎是合适的。这些要求基于参与本研究的墨西哥儿童的体重。联合国粮食及农业组织计算出 10 岁儿童的平均体重为 25 公斤。使用较高的平均体重，1-10 岁儿童的碘需求量为 90 - 120 μg/day。

16.4.3 成人

青少年和成人每天要求 150 μg/day 的碘是合理的，因为它对应于非流行地区（即碘摄入量充足的地区）每天尿液中碘的排泄量和食物中的碘含量 （22， 23）。它还提供必要的碘摄入量，以将血浆碘化物水平维持在 0.10μg/dl 的临界限度以上，这是可能与甲状腺肿发作相关的平均水平 （24）。此外，需要这种碘摄入量水平才能将甲状腺的碘储存保持在 10 毫克的临界阈值以上，低于该阈值，甲状腺球蛋白碘化水平不足会导致甲状腺激素合成紊乱 （23）。

反映碘平衡或其对甲状腺生理学影响的数据有助于确定最佳碘摄入量。在摄入足量碘的成人和青少年中，大多数膳食碘最终会出现在尿液中；因此，尿碘浓度是评估碘摄入量的有用指标 （1， 23）。为此，如果收集

了足够多的样本并且它们准确地代表了一个社区，那么随意样本就足够了（14，25）。A 尿碘100 μg/l 的浓度相当于成人每天摄入约 150 μg/day。人群中位尿碘浓度低于 100 μg/day 与甲状腺中位大小增加有关，并且可能与血清 TSH 和甲状腺球蛋白值增加有关。纠正碘缺乏症将使所有这些措施恢复到正常范围。来自欧洲 Thyro-Mobil 项目的最新数据证实了这些关系，表明最大的甲状腺大小与最低的尿碘浓度相关 （26）。一旦达到中位尿碘排泄量约 100 μg/l，甲状腺大小与体型的比率保持相当稳定。Moμlopoμlos 等人 （27） 报道，尿碘排泄量在 151 至 200 μg/g 肌酐(1.18-1.57 μmol/g 肌酐)之间,对应于约 200 μg/l(1.57 μmol/l)的浓度，与非甲状腺肿性人群中血清 TSH 的最低值相关。同样，来自澳大利亚的最新数据显示，最低的血清 TSH 和甲状腺球蛋白值与尿液中含有 200-300 μg 碘/g 肌酐（1.57-2.36 μmol 碘/g 肌酐）有关（28）。

其他研究跟踪了没有甲状腺的成年受试者的血清 TSH 水平，这些受试者接受了分级剂量的 T4，发现平均每日剂量为 100 μg 的 T4 需要至少 65 μg 的碘才能被甲状腺以最大效率使用，以建立甲状腺功能正常。在实践中，从未获得过如此高的效率，因此需要相当多的碘。来自对照观察的数据将低尿碘浓度与高甲状腺肿患病率、高放射性碘摄取和低甲状腺有机碘含量联系起来 （12）。一旦尿碘排泄量达到 100μg/l （0.78 μmol/l） 或更高，这些测量值中的每一种都达到稳定状态。

16.4.4 *孕妇*

怀孕期间的碘需求量增加，以满足胎儿的需要，并补偿由于怀孕期间碘的肾脏清除率增加而导致的尿液中碘损失的增加 （29）。以前，要求来

自妊娠期和中度碘缺乏条件下新生儿甲状腺功能的研究。例如，在比利时，碘摄入量估计为 50-70 μg/day（30），怀孕期间甲状腺功能的特点是血清游离甲状腺激素浓度逐渐降低，血清 TSH 和甲状腺球蛋白增加。甲状腺体积显著增加，10% 的妇女在妊娠结束时超过正常上限。新生儿的血清 TSH 和甲状腺球蛋白高于母亲 （31）。只有 预防这些异常当母亲在怀孕期间每天补充 161 /day 的碘化物（来自每天 131 μg 碘化钾和 100 μg T4）（32）。T4 与碘一起给予孕妇以快速纠正亚临床甲状腺功能减退症，如果单独服用碘，则不会发生这种情况。这些数据表明，预防怀孕期间母亲和胎儿亚临床甲状腺功能减退症发作，从而防止胎儿脑损伤的可能风险所需的碘摄入量约为 200 μg/day。

根据上述对各自人群的考虑，专家磋商会得出结论，世卫组织/联合国儿童基金会/国际碘缺乏病控制委员会（WHO/UNICEF/ICCIDD）关于每日碘摄入量的建（14）是最好的选择，目前没有理由改变它们。表 16.4 总结了目前的碘摄入量建议。

表 16.4

世界卫生组织、联合国儿童基金会和国际碘缺乏病控制委员会（WHO/UNICEF/ICCIDD）的每日碘摄入量建议

群	碘摄入量	
	（μg/day）	（μg/kg/day）
婴儿和儿童，0-59 个月	90	6.0－30.0
儿童，6-12 岁	120	4.0
青少年和成人，从 13 岁到成年	150	2.0
孕妇	200	3.5
哺乳期妇女	200	3.5

来源：参考文献 （14）。

根据上述对各自人群的考虑，专家磋商会得出结论，世卫组织/联合国儿童基金会/国际碘缺乏病控制委员会（WHO/UNICEF/ICCIDD）关于每日碘摄入量的建议（14）是最好的选择，目前没有理由改变它们。表 16.4 总结了目前的碘摄入量建议。

16.5 上限

虽然确保甲状腺功能正常需要生理量的碘，但大量过量的碘会抑制甲状腺激素的合成和释放过程（Wolff Chaikoff 效应）（33）。碘摄入量的阈值上限（超过该摄入量后甲状腺功能受到抑制）并不容易定义，因为它受碘过量摄入前的碘摄入量水平的影响。事实上，长期的中度碘缺乏症伴随着碘化物的加速捕获和甲状腺内碘储存的减少 23）。在这些条件下，甲状腺内碘和总碘之间的临界比值是 Wolff Chaikoff 效应的起点，在膳食碘供应不足的情况下比正常情况下更容易达到。此外，新生儿甲状腺对 Wolff-Chaikoff 效应特别敏感，因为未成熟的甲状腺无法减少血浆中碘的摄取以补偿碘摄入量的增加 （34）。因此，碘摄入量的上限将取决于碘摄入量的基础状态和年龄。

16.5.1 中度碘缺乏地区的碘摄入量

在比利时的一项研究中，母亲的碘超负荷（由于使用皮肤聚维酮碘进行硬膜外麻醉或剖宫产所致）增加了妇女的乳汁碘浓度，并增加了足月新生儿（平均体重约 3 公斤）的尿碘排泄量 （35）。在没有碘超负荷的情况下，母乳中的平均碘含量为 9μg/dl （0.63 μmol/l），婴儿出生后 5 天尿碘为 12μg/dl （0.94 μmol/l）。母亲使用聚维酮碘进行硬膜外麻醉或剖宫产后，平均乳碘浓度为 18 和 128 μg/dl，与婴儿尿碘排泄水

平分别为 280 和 1840 μg/l（2.20-14.48 μmol/l）相关 （35）。根据每天摄入约 6.5 dl 母乳，碘超负荷母亲的婴儿的平均碘摄入量估计分别为 117 和 832 μg/day，或 39 和 277 μg/kg/day。较低剂量显着增加了对外源性甲状腺释放激素的峰值 TSH 反应，但没有增加 TSH 反应曲线下的（分泌）面积。较高的剂量增加了峰反应和分泌面积以及基线 TSH 浓度。然而，血清 T4 浓度没有改变 （35）。因此，这些婴儿处于轻度和短暂的代偿性甲状腺功能减退状态。更普遍地说，母亲在分娩时使用聚维酮碘会增加新生儿 TSH 和筛查先天性甲状腺功能减退症时的召回率 （36）。这些数据表明，在相对膳食碘缺乏地区（比利时）的新生儿期中度碘超负荷会损害甲状腺激素的形成。

同样，法国和德国的研究表明，暴露于皮肤聚维酮碘或荧光醇碘溶液的早产儿，以及尿液中碘排泄超过 100 μg/day，表现为血清中 T4 降低和 TSH 浓度增加 （37， 38）。这些变化的程度在妊娠不足 34 周的早产儿中比在妊娠 35-37 周的早产儿中更为明显。婴儿一词不受影响。

这些研究表明，在欧洲，碘摄入量的上限容易导致新生儿甲状腺分泌受阻，尤其是在成熟婴儿（即每天约 120 μg/day，每天 40 μg/kg/day）仅比正常母乳的平均摄入量高 1.5 至 3 倍，与推荐摄入量的上限大致相等。

16.5.2 碘充足地区的碘摄入量

美国尚未进行类似的研究，由于美国的碘摄入量要高得多，美国的短暂性甲状腺功能减退症比欧洲低八倍 （39）。例如，新生儿尿液浓度为 50 μg/dl 及以上，这可能对应于欧洲的 Wolff-Chaikoff 效应，在北美的

健康新生儿中很常见 （15， 16）。

1978 年美国婴儿的平均碘摄入量，包括喂养全脂牛奶的婴儿，通过市场篮子法 （40） 估计为 576 μg/day （标准差 [SD]，196），幼儿为 728 μg/day （SD， 315），成人为 952 μg/day （SD， 589）。婴儿的上限摄入量（968 μg/day）将为 7 公斤重的婴儿提供 138 μg/kg/day 的每日摄入量，幼儿的上限摄入量（1358 微克/天）将为 15 公斤重的幼儿提供 90 μg/kg 的每日摄入量。

表 16.5 总结了各组推荐的碘膳食摄入量上限，在欧洲研究中，这似乎没有损害 Delange 婴儿组的甲状腺功能;在美国的负荷研究中，在成人中;或在美国摄入时对膳食摄入量的最高估计值 （40）。除了对碘过量过敏的早产儿的值外，表 16.5 中列出的可能安全上限比推荐摄入量高 15-20 倍。这些数据请参阅碘摄入量的所有来源。婴儿配方奶粉的平均碘含量约为 5μg/dl。上限可能应该是提供每日碘摄入量不超过 100 μg/kg 的上限。假设总摄入量来自婴儿配方奶粉并且每日牛奶摄入量为 150ml/kg (100kcal/kg)，婴儿配方奶粉中碘含量的上限约为 65μg/dl 升。因此，目前建议的婴儿配方奶粉中碘的上限为 75mg/100kcal（89mg/500kJ or 50μg/dl），这似乎是合理的。

表 16.5

各组别的推荐膳食碘摄入量及碘摄入量上限

群	建议摄入量（μg/kg/天）	上限[a]（μg/kg/天）
婴儿和儿童		
早产儿	30	100
0-6 个月	15	150
7-12 个月	15	140
1-6 岁	6	50
7-12 岁	4	50
青少年和成人（13+ 岁）	2	30
孕妇	3.5	40
哺乳期妇女	3.5	40

a 可能安全。

来源：改编自参考文献 （18）。

16.5.3 碘摄入过量

在碘含量充足的地区，健康成年人的碘摄入过量很难定义。许多人经常接触大量的碘——10-200 mg/day——没有明显的副作用。常见来源是药物（例如每 200 mg 胶囊含有 75 mg 碘）、食物（尤其是乳制品）、海带（在日本大量食用）和含碘染料（用于放射学检查）。有时，这些中的每一个都可能对甲状腺产生显着影响，但通常，它们可以毫无困难地耐受。Braverman 等人 （41） 表明，没有潜在甲状腺疾病证据的人在面对大量过量的碘时几乎总是保持甲状腺功能正常，并逃避了甲状腺内过量碘对碘化物的组织（即氧化碘物质附着在甲状腺中的酪氨酸残基上，以实现甲状腺激素的合成）和随后的激素合成（逃避， 或适应急性 Wolff-Chaikoff 效应）。这种适应很可能涉及甲状腺碘化物捕获的减少，可能是对最近克隆的甲状腺碘化钠转运蛋白减少的反应 （42）。

健康碘充足成年人对大剂量碘的耐受性是 WHO 在 1994 年表示“每日碘摄入量高达 1 mg，即 1000 μg，似乎是完全安全的”（43）的原因。当然，这种说法不包括新生儿和婴儿（由于之前讨论过的因素）。此外，必须考虑到碘过量会诱发甲状腺炎患者的甲状腺功能减退症 （44），并且在自主甲状腺结节患者碘供应突然和过度增加的情况下会诱发甲状腺功能亢进症 （3， 4， 45）。最后，碘过量可触发遗传易感动物和个体的甲状腺自身免疫，并可能通过增加状-滤泡状甲状腺癌的比例来改变甲状腺癌的模式 （46）。

总之，很明显，纠正碘缺乏的好处远远大于补碘的风险 （46， 47）。

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16. Iodine

16.1 Role of iodine in human metabolic processes

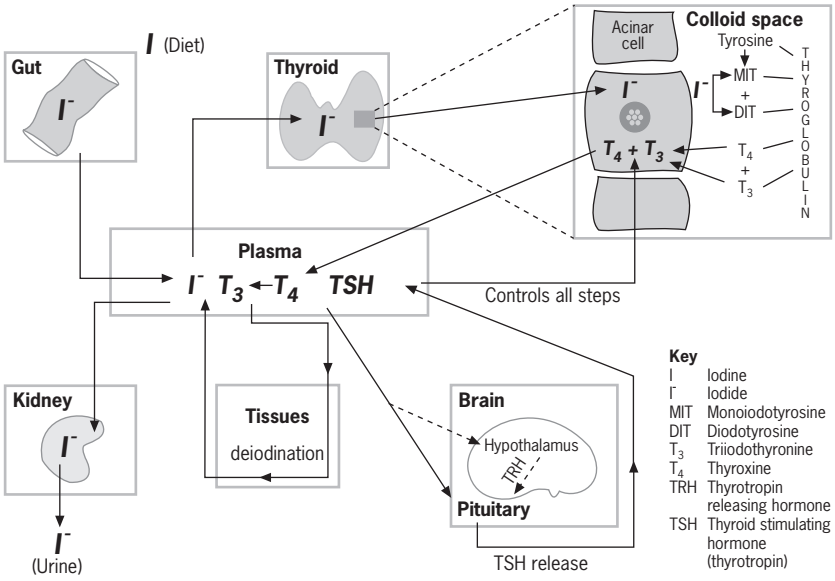
At present, the only physiological role known for iodine in the human body is in the synthesis of thyroid hormones by the thyroid gland. Therefore, the dietary requirement of iodine is determined by normal thyroxine (T_4) production by the thyroid gland without stressing the thyroid iodide trapping mechanism or raising thyroid stimulating hormone (TSH) levels.

Iodine from the diet is absorbed throughout the gastrointestinal tract. Dietary iodine is converted into the iodide ion before it is absorbed. The iodide ion is 100% bioavailable and absorbed totally from food and water. This is, however, not true for iodine within thyroid hormones ingested for therapeutic purposes.

Iodine enters the circulation as plasma inorganic iodide, which is cleared from the circulation by the thyroid and kidney. The iodide is used by the thyroid gland for synthesis of thyroid hormones, and the kidney excretes excess iodine with urine. The excretion of iodine in the urine is a good measure of iodine intake. In a normal population with no evidence of clinical iodine deficiency either in the form of endemic goitre or endemic cretinism, urinary iodine excretion reflects the average daily iodine requirement. Therefore, for determining the iodine requirements and the iodine intake, the important indexes are serum T_4 and TSH levels (exploring thyroid status) and urinary iodine excretion (exploring iodine intake). A simplified diagram of the metabolic circuit of iodine is given in Figure 16.1.

All biological actions of iodide are attributed to the thyroid hormones. The major thyroid hormone secreted by the thyroid gland is T_4. T_4 in circulation is taken up by the cells and is de-iodinated by the enzyme 5′-monodeiodinase in the cytoplasm to convert it into triiodothyronine (T_3), the active form of thyroid hormone. T_3 traverses to the nucleus and binds to the nuclear receptor. All the biological actions of T_3 are mediated through the binding to the nuclear receptor, which controls the transcription of a particular gene to bring about the synthesis of a specific protein.

FIGURE 16.1
Summary of thyroid hormone production and regulation



Source: reference (*1*).

The physiological actions of thyroid hormones can be categorized as 1) growth and development and 2) control of metabolic processes in the body. Thyroid hormones play a major role in the growth and development of the brain and central nervous system in humans from the 15th week of gestation to 3 years of age. If iodine deficiency exists during this period and results in thyroid hormone deficiency, the consequence is derangement in the development of the brain and central nervous system. These derangements are irreversible; the most serious form being that of cretinism. The effect of iodine deficiency at different stages of life is given in Table 16.1.

The other physiological role of thyroid hormones is to control several metabolic processes in the body. These include carbohydrate, fat, protein, vitamin, and mineral metabolism. For example, thyroid hormone increases energy production, increases lipolysis, and regulates neoglucogenesis, and glycolysis.

16.2 Populations at risk for iodine deficiency

Iodine deficiency affects all populations at all stages of life, from the intrauterine stage to old age, as shown in Table 16.1. However, pregnant women, lactating women, women of reproductive age, and children younger than 3

TABLE 16.1
Effects of iodine deficiency, by life stage

Life stage	Effects
Fetus	Abortions Stillbirths Congenital anomalies Increased perinatal mortality Increased infant mortality Neurological cretinism: mental deficiency, deaf mutism, spastic diplegia, and squint Myxedematous cretinism: mental deficiency, hypothyroidism and dwarfism Psychomotor defects
Neonate	Neonatal goitre Neonatal hypothyroidism
Child and adolescent	Goitre Juvenile hypothyroidism Impaired mental function Retarded physical development
Adult	Goitre with its complications Hypothyroidism Impaired mental function Iodine-induced hyperthyroidism

Sources: adapted from references (*2–4*).

years of age are considered the most important groups in which to diagnose and treat iodine deficiency (*2*, *5*), because iodine deficiency occurring during fetal and neonatal growth and development leads to irreversible damage of the brain and central nervous system and, consequently, to irreversible mental retardation.

16.3 Dietary sources of iodine

The iodine content of food depends on the iodine content of the soil in which it is grown. The iodine present in the upper crust of the earth is leached by glaciation and repeated flooding, and is carried to the sea. Seawater is, therefore, a rich source of iodine (*6*). The seaweed located near coral reefs has an inherent biological capacity to concentrate iodine from the sea. The reef fish which thrive on seaweed are also rich in iodine. Thus, a population consuming seaweed and reef fish will have a high intake of iodine, as is the case in Japan. Iodine intakes by the Japanese are typically in the range of 2–3 mg/day (*6*). In several areas of Africa, Asia, Latin America, and parts of Europe, iodine intake varies from 20 to 80 µg/day. In Canada and the United States and some parts of Europe, the intake is around 500 µg/day. The average iodine content

TABLE 16.2
Average iodine content of foods (μg/kg)

	Fresh basis		Dry basis	
Food	Mean	Range	Mean	Range
Fish (fresh water)	30	17–40	116	68–194
Fish (marine)	832	163–3180	3715	471–4591
Shellfish	798	308–1300	3866	1292–4987
Meat	50	27–97	—	—
Milk	47	35–56	—	—
Eggs	93	—	—	—
Cereal grains	47	22–72	65	34–92
Fruits	18	10–29	154	62–277
Legumes	30	23–36	234	223–245
Vegetables	29	12–201	385	204–1636

Source: reference (*6*).

TABLE 16.3
Iodine content of selected environmental media

Medium	Iodine content
Terrestrial air	1 μg/l
Marine air	100 μg/l
Terrestrial water	5 μg/l
Sea water	50 μg/l
Igneous rocks	500 μg/kg
Soils from igneous rocks	9000 μg/kg
Sedimentary rocks	1500 μg/kg
Soils from sedimentary rocks	4000 μg/kg
Metamorphic rocks	1600 μg/kg
Soils from metamorphic rocks	5000 μg/kg

Source: reference (*6*).

of foods (fresh and dry basis) as reported by Koutras et al. (*6*) is given in Table 16.2.

The iodine content of food varies with geographic location because there is a large variation in the iodine content of the various environmental media (Table 16.3) (*6*). Thus, the average iodine content of foods shown in Table 16.2 cannot be used universally for estimating iodine intake.

16.4 Recommended intakes for iodine

The daily intake of iodine recommended by the Food and Nutrition Board of the United States National Academy of Sciences in 1989 was 40 μg/day for young infants (0–6 months), 50 μg/day for older infants (7–12 months), 60–100 μg/day for children (1–10 years), and 150 μg/day for adolescents and

adults (*7*). These values approximate to 7.5 µg/kg/day for infants aged 0–12 months, 5.4 µg/kg/day for children aged 1–10 years, and 2 µg/kg/day for adolescents and adults. These amounts are proposed to allow normal T_4 production without stressing the thyroid iodide trapping mechanism or raising TSH levels.

16.4.1 Infants

The recommendation of 40 µg/day for infants aged 0–6 months (or 8 µg/kg/day, 7 µg/100 kcal, or 50 µg/l milk) is probably based on the observation reported in the late 1960s that the iodine content of human milk was approximately 50 µg/l and the assumption that nutrition of the human-milk-fed infant growing at a satisfactory rate represents an adequate level of nutrient intake (*8*, *9*). However, recent data indicate that the iodine content of human milk varies markedly as a function of the iodine intake of the population (*10*). For example, it ranges from 20 to 330 µg/l in Europe and from 30 to 490 µg/l in the United States (*8*, *10*, *11*). It is as low as 12 µg/l in populations experiencing severe iodine deficiency (*8*, *10*). On this basis, an average human-milk intake of 750 ml/day would give an intake of iodine of about 60 µg/day in Europe and 120 µg/day in the United States. The upper United States value (490 µg/l) would provide 368 µg/day or 68 µg/kg/day for a 5-kg infant.

Positive iodine balance in the young infant, which is required for increasing the iodine stores of the thyroid, is achieved only when the iodine intake is at least 15 µg/kg/day in term infants and 30 µg/kg/day in pre-term infants (*12*). The iodine requirement of pre-term infants is twice that of term infants because of a much lower retention of iodine by pre-term infants (*8*, *12*). Based on the assumption of an average body weight of 6 kg for a child of 6 months, 15 µg/kg/day corresponds approximately to an iodine intake and requirement of 90 µg/day. This value is twofold higher than the present United States recommendations.

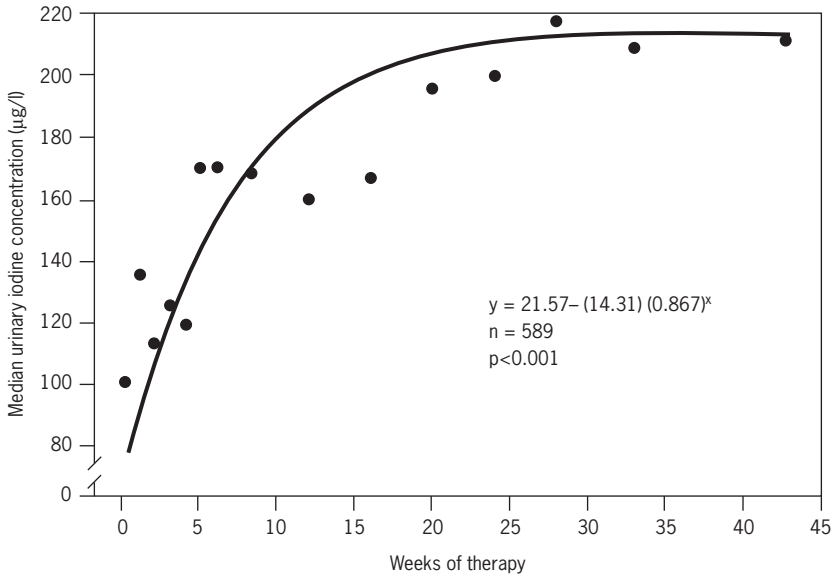
On the basis of these considerations, The World Health Organization (WHO) in 2001 updated its 1996 recommendations (*13*) and proposed, together with the United Nations Children's Fund (UNICEF) and the International Council for Control of Iodine Deficiency Disorders (ICCIDD), an iodine intake of 90 µg/day from birth onwards (*14*). To reach this objective, and based on an intake of milk of about 150 ml/kg/day, it was further proposed that the iodine content of formula milk be increased from 50 µg/l, the former recommendation, to 100 µg/l for term infants and to 200 µg/l for pre-term infants.

For a urine volume of about 4–6 dl/day, the urinary concentration of iodine indicating iodine repletion should be in the range of 150–220 µg/l

(1.18–1.73 µmol/l) in infants aged 0–3 years. Such values have been observed in iodine-replete infants in Europe (*15*), Canada (*16*), and the United States (*16*). Under conditions of moderate iodine deficiency, as seen in Belgium for example, the average urinary iodine concentration is only 100 µg/l (0.80 µmol/l) in this age group. It reaches a stable normal value of about 200 µg/l (1.57 µmol/l) only from the 30th week of daily iodine supplementation with a physiological dose of 90 µg/day (*17*, *18*) (Figure 16.2).

When the urinary iodine concentration in neonates and young infants is below a threshold of 50–60 µg/l (0.39–0.47 µmol/l), corresponding to an intake of 25–35 µg/day, there is a sudden increase in the prevalence of neonatal serum TSH values in excess of 50 mU/ml, indicating subclinical hypothyroidism, eventually complicated by transient neonatal hypothyroidism (*19*). When the urinary iodine concentration is in the range of 10–20 µg/l (0.08–0.16 µmol/l), as observed in populations with severe endemic goitre, up to 10% of the neonates have overt severe hypothyroidism, with serum TSH levels above 100 mU/ml and serum T_4 values below 30 µg/l (39 nmol/l) (*19*). Left untreated, these infants will develop myxedematous endemic cretinism (*20*).

FIGURE 16.2
Changes over time in the median urinary concentration of iodine in healthy Belgian infants aged 6–36 months and supplemented with iodine at 90 µg/kg/day for 44 weeks (each point represents 32–176 iodine determinations)



Source: reference (*18*).

Overall, existing data point to an iodine requirement of the young infant of 15 µg/kg/day (30 µg/kg/day in pre-term infants). Hyperthyrotropinaemia (high levels of serum TSH), indicating subclinical hypothyroidism with the risk of brain damage, occurs when the iodine intake is about one third of this value, and dramatic neonatal hypothyroidism, resulting in endemic cretinism, occurs when the intake is about one tenth of this value.

16.4.2 Children

The daily iodine requirement on a body weight basis decreases progressively with age. A study by Tovar and colleagues (*21*) correlating 24-hour thyroid radioiodine uptake and urinary iodine excretion in 9–13-year-old schoolchildren in rural Mexico suggested that an iodine intake in excess of 60 µg/day is associated with a 24-hour thyroidal radioiodine uptake below 30%. Lower excretion values are associated with higher uptake values. An iodine intake of 60 µg/day is equivalent to 3 µg/kg/day in an average size 10-year-old child (approximate body weight of 20 kg). An intake of 60–100 µg/day for a child of 1–10 years thus seems appropriate. These requirements are based on the body weight of Mexican children who participated in this study. The Food and Agriculture Organization of the United Nations calculates the average body weight of a 10-year-old child as being 25 kg. Using the higher average body weight, the iodine requirement for a 1–10-year-old child would be 90–120 µg/day.

16.4.3 Adults

A requirement for iodine of 150 µg/day for adolescents and adults is justified by the fact that it corresponds to the daily urinary excretion of iodine and to the iodine content of food in non-endemic areas (i.e. in areas where iodine intake is adequate) (*22*, *23*). It also provides the iodine intake necessary to maintain the plasma iodide level above the critical limit of 0.10 µg/dl, which is the average level likely to be associated with the onset of goitre (*24*). Moreover, this level of iodine intake is required to maintain the iodine stores of the thyroid above the critical threshold of 10 mg, below which an insufficient level of iodination of thyroglobulin leads to disorders in thyroid hormone synthesis (*23*).

Data reflecting either iodine balance or its effect on thyroid physiology can help to define optimal iodine intake. In adults and adolescents who consume adequate amounts of iodine, most dietary iodine eventually appears in the urine; thus, the urinary iodine concentration is a useful measure for assessing iodine intake (*1*, *23*). For this, casual samples are sufficient if enough are collected and if they accurately represent a community (*14*, *25*). A urinary iodine

concentration of 100 µg/l corresponds to an intake of about 150 µg/day in the adult. Median urinary iodine concentrations below 100 µg/l in a population are associated with increases in median thyroid size and possibly in increases in serum TSH and thyroglobulin values. Correction of the iodine deficiency will bring all these measures back into the normal range. Recent data from the Thyro-Mobil project in Europe have confirmed these relationships by showing that the largest thyroid sizes are associated with the lowest urinary iodine concentrations (*26*). Once a median urinary iodine excretion of about 100 µg/l is reached, the ratio of thyroid size to body size remains fairly constant. Moulopoulos et al. (*27*) reported that a urinary iodine excretion between 151 and 200 µg/g creatinine (1.18–1.57 µmol/g creatinine), corresponding to a concentration of about 200 µg/l (1.57 µmol/l), correlated with the lowest values for serum TSH in a non-goitrous population. Similarly, recent data from Australia show that the lowest serum TSH and thyroglobulin values were associated with urine containing 200–300 µg iodine/g creatinine (1.57–2.36 µmol iodine/g creatinine) (*28*).

Other investigations followed serum TSH levels in adult subjects without thyroid glands who were given graded doses of T_4 and found that an average daily dose of 100 µg T_4 would require at least 65 µg of iodine to be used with maximal efficiency by the thyroid in order to establish euthyroidism. In practice, such maximal efficiency is never obtained and therefore considerably more iodine is necessary. Data from controlled observations associated a low urinary iodine concentration with a high goitre prevalence, high radioiodine uptake, and low thyroidal organic iodine content (*12*). Each of these measures reached a steady state once the urinary iodine excretion was 100 µg/l (0.78 µmol/l) or greater.

16.4.4 Pregnant women

The iodine requirement during pregnancy is increased to provide for the needs of the fetus and to compensate for the increased loss of iodine in the urine resulting from an increased renal clearance of iodine during pregnancy (*29*). Previously, requirements have been derived from studies of thyroid function during pregnancy and in the neonate under conditions of moderate iodine deficiency. For example, in Belgium, where the iodine intake is estimated to be 50–70 µg/day (*30*), thyroid function during pregnancy is characterized by a progressive decrease in the serum concentrations of free-thyroid hormones and an increase in serum TSH and thyroglobulin. Thyroid volume progressively increases and is above the upper limit of normal in 10% of the women by the end of pregnancy. Serum TSH and thyroglobulin are higher in the neonates than in the mothers (*31*). These abnormalities are prevented only

TABLE 16.4
Daily iodine intake recommendations by the World Health Organization, United Nations Children's Fund, and International Council for Control of Iodine Deficiency Disorders

Group	Iodine intake (μg/day)	Iodine intake (μg/kg/day)
Infants and children, 0–59 months	90	6.0–30.0
Children, 6–12 years	120	4.0
Adolescents and adults, from 13 years of age through adulthood	150	2.0
Pregnant women	200	3.5
Lactating women	200	3.5

Source: reference (*14*).

when the mother receives a daily iodide supplementation of 161 μg/day during pregnancy (derived from 131 μg potassium iodide and 100 μg T_4 given daily) (*32*). T_4 was administered with iodine to the pregnant women to rapidly correct subclinical hypothyroidism, which would not have occurred if iodine had been administered alone. These data indicate that the iodine intake required to prevent the onset of subclinical hypothyroidism of mother and fetus during pregnancy, and thus to prevent the possible risk of brain damage of the fetus, is approximately 200 μg/day.

On the basis of the above considerations for the respective population groups, the Expert Consultation concluded that the WHO/UNICEF/ICCIDD recommendations for daily iodine intakes (*14*) were the best available and saw no grounds for altering them at the present time. The current intake recommendations for iodine are summarized in Table 16.4.

16.5 Upper limits

While a physiological amount of iodine is required for insuring a normal thyroid function, a large excess of iodine can be harmful to the thyroid by inhibiting the process of synthesis and release of thyroid hormones (Wolff-Chaikoff effect) (*33*). The threshold upper limit of iodine intake (the intake beyond which thyroid function is inhibited) is not easy to define because it is affected by the level of iodine intake before exposure to iodine excess. Indeed, long-standing moderate iodine deficiency is accompanied by an accelerated trapping of iodide and by a decrease in the iodine stores within the thyroid (*23*). Under these conditions, the critical ratio between iodide and total iodine within the thyroid, which is the starting point of the Wolff-Chaikoff effect, is more easily reached in conditions of insufficient dietary supply of iodine than under normal conditions. In addition, the neonatal

thyroid is particularly sensitive to the Wolff-Chaikoff effect because the immature thyroid gland is unable to reduce the uptake of iodine from the plasma to compensate for increased iodine ingestion (*34*). Consequently, the upper limit of iodine intake will depend on both basal status of iodine intake and age.

16.5.1 Iodine intake in areas of moderate iodine deficiency

In a study in Belgium, iodine overload of mothers (caused by use of cutaneous povidone iodine for epidural anaesthesia or caesarean section) increased the milk iodine concentration of women and increased urinary iodine excretion in their term newborn infants (mean weight about 3 kg) (*35*). In the absence of iodine overload, the mean iodine content of breast milk was 9 µg/dl (0.63 µmol/l) and the urinary iodine of the infant at 5 days of life was 12 µg/dl (0.94 µmol/l). After the use of povidone iodine in the mother for epidural anaesthesia or for caesarean section, the mean milk iodine concentrations were 18 and 128 µg/dl, and were associated with average infant urinary iodine excretion levels of 280 and 1840 µg/l (2.20–14.48 µmol/l), respectively (*35*). Based on an intake of some 6.5 dl of breast milk per day, the estimated average iodine intakes in the babies of iodine overload mothers were 117 and 832 µg/day, or 39 and 277 µg/kg/day, respectively. The lower dose significantly increased the peak TSH response to exogenous thyroid-releasing hormone but did not increase the (secretory) area under the TSH response curve. The higher dose increased the peak response and secretory area as well as the baseline TSH concentration. Serum T_4 concentrations were not altered, however (*35*). Thus, these infants had a mild and transient, compensated hypothyroid state. More generally, the use of povidone iodine in mothers at the time of delivery increased neonatal TSH and the recall rate at the time of screening for congenital hypothyroidism (*36*). These data indicate that modest iodine overloading of term infants in the neonatal period in an area of relative dietary iodine deficiency (Belgium) can impair thyroid hormone formation.

Similarly, studies in France and Germany indicated that premature infants exposed to cutaneous povidone iodine or fluorescinated alcohol-iodine solutions, and excreting iodine in urine in excess of 100 µg/day, manifested decreased T_4 and increased TSH concentrations in serum (*37*, *38*). The extent of these changes was more marked in premature infants with less than 34 weeks gestation than in those with 35–37 weeks gestation. The term infants were not affected.

These studies suggest that in Europe, the upper limit of iodine intake which predisposes to blockage of thyroid secretion in neonates and especially in pre-

mature infants (i.e. from about 120 µg/day, 40 µg/kg/day) is only 1.5 to 3 times higher than the average intake from normal human milk and roughly equivalent to the upper range of recommended intake.

16.5.2 Iodine intake in areas of iodine sufficiency

Similar studies have not been conducted in the United States, where transient hypothyroidism is eight times lower than in Europe because iodine intake is much higher in the United States (*39*). For example, urinary concentrations of 50 µg/dl and above in neonates, which can correspond to a Wolff-Chaikoff effect in Europe, are frequently seen in healthy neonates in North America (*15*, *16*).

The average iodine intake of infants in the United States in 1978, including infants fed whole cow milk, was estimated by the market-basket approach (*40*) to be 576 µg/day (standard deviation [SD], 196); that of toddlers, 728 µg/day (SD, 315) and that of adults, 952 µg/day (SD, 589). The upper range for infants (968 µg/day) would provide a daily intake of 138 µg/kg for a 7-kg infant, and the upper range for toddlers (1358 µg/day) would provide a daily intake of 90 µg/kg for a 15-kg toddler.

Table 16.5 summarizes the recommended upper limits of dietary intake of iodine by group, which did not appear to impair thyroid function in the group of Delange infants in European studies; in adults in loading studies in the United States; or during ingestion of the highest estimates of dietary intake in the United States (*40*). Except for the value for premature infants who appear hypersensitive to iodine excess, the probable safe upper limits listed in Table 16.5 are 15–20 times higher than the recommended intakes. These data

TABLE 16.5
Recommended dietary intakes of iodine and upper limits, by group

Group	Recommended intake (µg/kg/day)	Upper limit[a] (µg/kg/day)
Infants and children		
Premature	30	100
0–6 months	15	150
7–12 months	15	140
1–6 years	6	50
7–12 years	4	50
Adolescents and adults (13+ years)	2	30
Pregnant women	3.5	40
Lactating women	3.5	40

[a] Probably safe.
Source: adapted from reference (*18*).

refer to all sources of iodine intake. The average iodine content of infant formulas is approximately 5 µg/dl. The upper limit probably should be one that provides a daily iodine intake of no more than 100 µg/kg. For this limit—with the assumption that the total intake is from infant formula—and with a daily milk intake of 150 ml/kg (100 kcal/kg), the upper limit of the iodine content of infant formula would be about 65 µg/dl. The current suggested upper limit of iodine in infant formula of 75 µg/100 kcal (89 µg/500 kJ or 50 µg/dl), therefore, seems reasonable.

16.5.3 Excess iodine intake

Excess iodine intake in healthy adults in iodine-replete areas is difficult to define. Many people are regularly exposed to huge amounts of iodine—in the range 10–200 mg/day—without apparent adverse effects. Common sources are medicines (e.g. amiodarone contains 75 mg iodine per 200-mg capsule), foods (particularly dairy products), kelp (eaten in large amounts in Japan), and iodine-containing dyes (for radiologic procedures). Occasionally, each of these may have significant thyroid effects, but generally, they are tolerated without difficulty. Braverman et al. (*41*) showed that people without evidence of underlying thyroid disease almost always remain euthyroid in the face of large amounts of excess iodine and escape the acute inhibitory effects of excess intrathyroidal iodide on the organification (i.e. attachment of oxidized iodine species to tyrosil residues in the thyroid gland for the synthesis of thyroid hormones) of iodide and on subsequent hormone synthesis (escape from, or adaptation to, the acute Wolff-Chaikoff effect). This adaptation most likely involves a decrease in thyroid iodide trapping, perhaps corresponding to a decrease in the thyroid sodium-iodide transporter recently cloned (*42*).

This tolerance to huge doses of iodine in healthy iodine-replete adults is the reason why WHO stated in 1994 that, "Daily iodine intakes of up to 1 mg, i.e. 1000 µg, appear to be entirely safe" (*43*). This statement, of course, does not include neonates and young infants (due to factors previously discussed). In addition, it has to be considered that iodine excess can induce hypothyroidism in patients affected by thyroiditis (*44*) and can induce hyperthyroidism in cases of a sudden and excessive increment of iodine supply in patients with autonomous thyroid nodules (*3, 4, 45*). Finally, iodine excess can trigger thyroid autoimmunity in genetically susceptible animals and individuals and may modify the pattern of thyroid cancer by increasing the ratio of papillary–follicular thyroid cancers (*46*).

In conclusion, it clearly appears that the benefits of correcting iodine deficiency far outweigh the risks of iodine supplementation (*46*, *47*).

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