Evira Research Reports 7/2008

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- a quantitative risk assessment

Finnish Food Safety Authority Evira

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Kuvailulehti

Julkaisija	Elintarviketurvallisuusvirasto Evira
Julkaisun nimi	Suomalaisten 1-, 3- ja 6-vuotiaiden lasten A-vitamiinin saanti maksaruokien välityksellä - kvantitatiivinen riskinarvointi
Tekijät	Kirsi-Helena Liukkonen, Tapani Lyytikäinen, Tero Hirvonen, Christina Bäckman, Carina Kronberg-Kippilä, Suvi Virtanen
Tiivistelmä	Maksa sisältää runsaasti A-vitamiinia ja monia muita ravintoaineita. Vaikka maksa on monipuolinen ruoka-aine, sen käytössä on myös haittansa. A-vitamiini esiintyy maksassa retinoidimuodossa, mikä voi jatkuvina suurina annoksina aiheuttaa myrkytyksen. Liiallisen A-vitamiinin saannin ehkäisemiseksi maksaruokia ei vuodesta 1990 lähtien ole suositeltu alle 1-vuotiaille. Leikki-ikäisten lasten maksaruokien (jauhemaksa- ja maksapihvi, maksakastike, maksalaatikko), maksamakkaran ja –pasteijan käyttöä on neuvottu rajoittamaan pariin kertaan kuukaudessa. Suositusten tarpeellisuuden arvioimiseksi Elintarviketurvallisuusvirasto Evirassa tehtiin riskinarviointi suomalaislasten A-vitamiinin saannista maksaruokien välityksellä. Riskinarvioinnin tavoitteena oli arvioida 1-, 3- ja 6-vuotiaiden lasten altistumista maksaruokien retinoidimuotoiselle A-vitamiinille sekä samalla selvittää, tuleeko lasten maksaruokien käyttöä edelleen rajoittaa. Riskinarvioinnissa käytettiin maksaruokien kulutustietoja (DIPP-ravintotutkimus) sekä resepti- ja retinoidipitoisuustietoja. Monte Carlo -simulaatiolla arvioitiin A-vitamiinin ja retinoidien saantia maksaruoista sekä ilman maksaruokien käyttöä. Altistusta arvioitiin pitkäaikaissaantina sekä altistuksena kerta-annoksesta. Simulointituloksia verrattiin saantisuosituksiin ja saannin ylärajoihin. Simulointimallin avulla arvioitiin myös maksaruokien turvallista annoskokoa ja syöntitiheyttä. Riskinarvioinnissa tehtiin seuraavat johtopäätökset: 1. Vaikka maksansyönti auttaa joitain lapsia A-vitamiinin saantisuositusten täyttymisessä, se voi altistaa toisia lapsia liian suurille retinoidipitoisuuksille. 2. Todellisten maksansyöjien osuus on hyvin todennäköisesti suurempi kuin kolmen päivän ruoankäyttötietojen perusteella voidaan olettaa. 3. Tarkasteltaessa maksaruokien pitkäaikaiskäytön turvallisuutta todetaan, että annoskoon lisäksi syöntitiheydellä on keskeinen merkitys. Yksivuotias voi turvallisesti syödä maksamakkaraa tai –pasteijaa ja kolme- ja kuusivuotias kaikkia maksaruokia, kunhan syöntitiheys ei ole liian suuri. Turvallinen annoskoko ja syöntitiheys riippuvat lapsen iästä ja maksaruuasta. Yleisesti maksamakkaraa ja –pasteijaa voi käyttää useammin kuin maksalaatikkoa, maksakastiketta tai maksapihvejä.

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Författare	Kirsi-Helena Liukkonen, Tapani Lyytikäinen, Tero Hirvonen, Christina Bäckman, Carina Kronberg-Kippilä, Suvi Virtanen
Resumé	Lever innehåller rikligt med A-vitamin och flera andra näringsämnen. Även om lever är ett mångsidigt födoämne finns det också nackdelar med att äta lever. A-vitamin förekommer i lever i form av retinoider som kan orsaka förgiftning genom kontinuerligt högt intag. För att undvika ett för högt intag av A-vitamin har leverrätter inte rekommenderats till barn under 1 år sedan 1990. Det har rekommenderats att konsumtionen av leverrätter (biff på mald lever och leverbiff, leversås och leverlåda), leverkorv och –pastej hos barn i lekåldern begränsas till ett par gånger i månaden. För att bedöma nödvändigheten av rekommendationerna har Livsmedelssäkerhetsverket Evira gjort en riskbedömning av finländska barns intag av A-vitamin från leverrätter. Målsättningen med riskbedömningen var att bedöma hur 1-, 3- och 6-åriga barn exponeras för A-vitamin i form av retinoider från leverrätter och att bedöma om barnens intag av leverrätter fortfarande skall begränsas. Vid riskbedömningen användes uppgifter om konsumtion av leverrätter (DIPP-nutritionsundersökning) samt receptinformation och uppgifter om retinoidnivåer. Intaget av A-vitamin och retinoider från leverrätter och även intag utan konsumtion av leverrätter bedömdes med hjälp av Monte Carlo-simulering. Exponeringen bedömdes som långtidsintag och som exponering från en engångsdos. Simuleringsresultaten jämfördes med rekommendationerna för intag och med de övre gränserna för intaget. Med hjälp av simuleringsmodellen beräknades också en trygg portionsstorlek och konsumtionsfrekvens. Utgående från riskbedömningen drogs följande slutsatser: 1. Även om konsumtion av lever hjälper vissa barn att uppnå rekommendationerna för intag av A-vitamin, så kan andra barn utsättas för alltför höga halter av retinoider. 2. Andelen verkliga leverkonsumenter är mycket sannolikt högre än vad som kan antas utgående från uppgifterna om tre dagars matkonsumtion. 3. Vid granskningen av säkerheten i långtidsintag av leverrätter är förutom portionens storlek också konsumtionsfrekvensen av central betydelse. En ettåring kan tryggt äta leverkorv eller –pastej och en treåring och en sexåring alla leverrätter, bara konsumtionsfrekvensen inte är för hög. Barnets ålder och leverrätten ifråga är avgörande för bedömningen av en trygg portionsstorlek och konsumtionsfrekvens. I allmänhet kan leverkorv och –pastej konsumeras oftare än leverlåda, leversås eller leverbiffar.

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Description

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Authors	Kirsi-Helena Liukkonen, Tapani Lyytikäinen, Tero Hirvonen, Christina Bäckman, Carina Kronberg-Kippilä, Suvi Virtanen

Abstract

Liver is a good source of vitamin A and many other nutrients. In addition to many beneficial effects, liver consumption also has some potential risks. One of them is that liver contains vitamin A in retinoid form, which can be toxic if ingested in large amounts on a continued basis.

In order to prevent excessive intake of vitamin A, liver-based foods have not been recommended for children under the age of one year since 1990. With toddlers, it has been advised that the consumption of liver-based foods (ground liver patties, liver steak, liver stew, liver casserole), liver sausage and liver pâté should be restricted to a couple of meals per month. To re-evaluate current recommendations, the Finnish Food Safety Authority, Evira has undertaken a risk assessment of retinoid intake from liver foods among Finnish children. The objectives of the risk assessment were to estimate the relevance of retinoid exposure from liver products among Finnish 1-, 3- and 6-year-old children and to assess whether children's consumption of liver foods still needs to be restricted.

The risk assessment was based on liver food consumption data (DIPP Nutrition Study), recipe information and analysis results of vitamin A (retinoids). To estimate intake by consumption of both non-liver and liver sources of vitamin A, Monte Carlo simulations were performed. The impact of liver consumption on the intake of vitamin A was estimated separately for single meal and daily long term average consumption. The simulation model results were compared with intake recommendations and upper intake limits. The models were also applied to estimate safe combinations of portion size and eating frequency for liver foods and their combinations.

Based on risk assessment, the following conclusions were made
1. Although consumption of liver foods helps to fulfil some children's daily vitamin A needs, there is a risk of intolerably high retinoid intake among other children.
2. Among children, the proportion of true eaters of liver foods is very probably higher than can be seen on the basis of 3-day food records.
3. When considering safe long term consumption of liver foods, in addition to portion size, eating frequency is an important factor. One-year-old children can eat safely liver sausage or pâté and 3- and 6-year-old children all liver foods as long as they do not do it too often. The safe portion size and eating frequency depends on the age group and type of liver food. In general, liver sausage or pâté can be eaten more often than liver casserole, liver sauce and liver patties.

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Definitions and abbreviations

Bioavailability
The fraction of the ingested dose of a compound that is available to mediate biological effects in the body.

CAC
Codex Alimentarius Commission

Carotenoids
Organic pigments naturally occurring in photosynthetic organisms. Some carotenoids are vitamin A precursors (provitamin A carotenoids).

Chylomicron
Large lipoprotein molecules that are created by the absorptive cells of the small intestine. Chylomicrons transport absorbed lipids to target tissues.

Food supplement
Foodstuffs the purpose of which is to supplement the normal diet, and which are concentrated sources of nutrients or other substances with a nutritional or physiological effect, alone or in combination, marketed in dose form, namely forms such as capsules, pastilles, tablets, pills and other similar forms, sachets of powder, ampoules of liquids, drop dispensing bottles, and other similar forms of liquids and powders designed to be taken in measured small unit quantities.

DIPP
The Finnish Type I Diabetes Prediction and Prevention study

EAR
Estimated average requirement. Nutrient intake value estimated to meet the average physiological requirement of the selected population group.

FAO
Food and Agriculture Organization of the United Nations

FNB
Food and Nutrition Board. Unit of the Institute of Medicine, part of the National Academy of Sciences, USA

IU
A unit of measurement for the amount of a substance, based on measured biological activity. For vitamin A, 1 IU equals the biological activity of 0.3 µg retinol (0.3 µg RE).

LOAEL
Lowest-observed-adverse-effect level

MAVIRA
Short for "Intake of vitamin A, cadmium and lead via liver foods among Finnish women of fertile age" – project.

NCM
Nordic Council of Ministers

NOAEL
No-observed-adverse-effect level

RBP
Retinol-binding protein

RAE
Retinol activity equivalent → Retinol equivalent

RE
→ Retinol equivalent

Retinoids
A class of chemical compounds consisting of a six-carbon ring structure with a polyprenoid side chain and a terminating carbon-oxygen functional group. In this risk assessment, the term refers to natural and synthetic retinoid derivatives with the biological activity of retinol.

Retinol equivalent
The specific biological activity of 1.0 microgram of all-trans retinol

Retinol
The most common natural retinoid (as free retinol or esterified to fatty acids), and the key molecule in body retinoid metabolism

RDI, RDA
Recommended dietary intake, recommended dietary allowance. The nutrient intake over time that theoretically would fulfil the needs of practically all (97.5 %) healthy individuals in a selected population group. RDI or RDA is calculated by adding a safety margin equal to two standard deviations to the estimated average requirement (EAR).

SCF
Scientific Committee on Food, European Commission

STRIP
Special Turku Coronary Risk Factor Intervention Project

UL
Upper tolerable level. The maximum daily intake of a nutrient unlikely to pose a risk of adverse health effects to humans.

US
United States

WHO
World Health Organisation of the United Nations

VAD
Vitamin A deficiency

Vitamin A
Retinoids and provitamin A carotenoids that exhibit the biological activity of retinol

VRN
National Nutrition Council, Valtion ravitsemusneuvottelukunta

Yhteenveto

A-vitamiini

A-vitamiini on välttämätön luonnossa esiintyvä rasvaliukoinen ravintoaine, jolla on tärkeä merkitys monissa biologisissa toiminnoissa, kuten näkökyky, solujen kasvu ja erilaistuminen, elimistön puolustusmekanismit ja sikiönkehitys. Sekä A-vitamiinin puute että liiallinen saanti voivat aiheuttaa terveyshaittoja. A-vitamiinin puute on harvinaista länsimaissa, mutta retinoidimuotoisen A-vitamiinin liikasaannin riski on olemassa. Sen sijaan karotenoidien liikasaannin ei ole osoitettu aiheuttavan A-vitamiinimyrkytystä.

Ihmiselimistö ei pysty itse valmistamaan A-vitamiinia, vaan se on saatava ravinnosta. Ravinnossa A-vitamiini esiintyy kahdessa muodossa: retinoideina eläinperäisissä ruoka-aineissa ja A-vitamiinin esiasteina karotenoideina kasvikunnan tuotteissa. Maksan retinoidipitoisuus on korkeampi kuin minkään muun ruoka-aineen. Retinoideja esiintyy myös ravintorasvoissa, rasvaisissa maitovalmisteissa, rasvaisissa kaloissa ja kananmunissa. Karotenoideja on vihreissä lehtivihanneksissa, keltaisissa kasviksissa ja keltaisissa ja oransseissa ei-sitrushedelmissä. Vitaminoidut elintarvikkeet ja ravintolisät voivat myös sisältää retinoidi- tai karotenoidimuotoista A-vitamiinia. Luonnollisten A-vitamiinilähteiden nauttiminen aiheuttaa harvoin myrkytystä. Poikkeuksena on liiallinen maksan, vitaminoitujen elintarvikkeiden ja ravintolisien jatkuva käyttö.

Projektin historia ja tavoitteet

Vuonna 1989 havaittiin suomalaisen sianmaksan sisältävän erittäin korkeita A-vitamiinipitoisuuksia. Retinoidien mahdollisten haittojen vuoksi on vuodesta 1990 lähtien raskaana olevia ja lapsia neuvottu rajoittamaan maksaruokien käyttöä. Vähentämällä A-vitamiinin käyttöä eläinten rehuissa ja terveydenhoidossa sianmaksan A-vitamiinipitoisuudet saatiin kuitenkin pian laskemaan. Raskaana oleville ja lapsille annettuja maksan käyttösuosituksia ei kuitenkaan muutettu.

Elintarviketurvallisuusvirastossa valmistui vuonna 2007 riskinarviointi hedelmällisessä iässä olevien suomalaisnaisten altistumisesta A-vitamiinille maksaruokien välityksellä (Mavira-projekti, Lavikainen ym. 2007). Riskinarviointiin perustuen viranomaiset päättivät lieventää maksan raskaudenaikaista käyttöä koskevia suosituksia. Riskinarviointi vahvisti, että pääruokina syötävien maksaruokien käyttöä raskauden aikana tulee edelleen välttää, mutta kohtuullinen maksamakkaran ja –pasteijan käyttö on kuitenkin turvallista.

Tämän riskinarvioinnin tavoitteena on arvioida 1-, 3- ja 6-vuotiaiden suomalaislasten retinoidien saantia maksaruokien välityksellä sekä samalla selvittää, onko maksaruokien käytön rajoittaminen lapsilla edelleen tarpeen.

Altistuksen arviointi

A-vitamiinin ja retinoidien saannin arvioimiseksi saatiin pitkäaikaisesta tyypin 1 diabeteksen ennustamis- ja ehkäisytutkimuksen (DIPP-tutkimus) ravintotutkimuksesta 963 yksivuotiaan, 835 kolmevuotiaan ja 850 kuusivuotiaan ruoankäyttötiedot. Lisäksi käytettiin sian-, naudan- ja broilerinmaksojen laboratorioanalyysejä sekä elintarviketeollisuudelta ja Kansanterveyslaitokselta saatuja resepti- ja markkinaosuustietoja.

Kerätyn tiedon perusteella rakennettiin Monte Carlo –simulaatiomalleja, joiden avulla arvioitiin lasten A-vitamiinin ja retinoidien saantia maksaruokien välityksellä ja ilman maksaruokia. Tu-

loksia verrattiin A-vitamiinin saantisuosituksiin ja retinoidien saantirajoihin. Malleja sovellettiin myös turvallisen maksaruokien annoskoon ja syöntitiheyden arviointiin.

Maksaruokien retinoidit

Retinoidien keskimääräinen pitoisuus oli korkein maksapihveissä (82 µg RE/g, vaihteluväli 15-806 RE/g). Seuraavina tulivat laskevassa järjestyksessä maksakastike (54 µg RE/g, vaihteluväli 12-474 RE/g), maksamakkara tai -pasteija (26 µg RE/g, vaihteluväli 8-59 µg RE/g) ja maksalaatikko (15 µg RE/g, vaihteluväli 10-41 µg RE/g). Retinoidipitoisuuksien vaihteluvälit heijastelivat vaihtelua sekä raaka-ainemaksojen retinoidipitoisuuksissa että reseptien koostumuksessa (maksan osuus).

A-vitamiinin ja retinoidien saanti

Noin 1 % yksivuotiaista ja 18 % kolme- ja kuusivuotiaista oli syönyt maksaruokia kolmen tutkimuspäivän aikana. Useimmin syöty maksaruoka oli maksamakkara tai –pasteija. Seuraavana tuli maksalaatikko. Vain muutamat lapset olivat syöneet maksakastiketta tai –pihvejä.

Maksan merkitys A-vitamiinin lähteenä oli ilmeinen, sillä maksansyöjillä keskimäärin 54-57 % retinoidien saannista ja 39-48 % A-vitamiinin saannista tulivat maksaruuista. Kaikilla maksansyöjillä keskimääräinen A-vitamiinin tarve (210 µg RE/päivä 1- ja 3-vuotiailla ja 275 µg RE/päivä 6-vuotiailla) täyttyi. Sen sijaan maksaa syömättömistä 1-vuotiaista 41 %:lla ja 3- ja 6-vuotiaista 10 %:lla A-vitamiinin saanti jäi alle keskimääräisen tarpeen.

Todelliset maksansyöjät

Kulutustietojen heikkoutena oli se, että ne eivät sisältäneet tietoa todellisten maksansyöjien ja maksaa syömättömien osuudesta. On hyvin todennäköistä, että osa vastaajista ei vain sattunut syömään maksaruokia niiden kolmen päivän aikana, jolloin ruokapäiväkirjat täytettiin. Tällöin todellinen maksaa syövien osuus tutkimusjoukossa olisi suurempi.

Kun todellisten maksansyöjien syöntitiheyttä ja osuutta arvioitiin zero-inflated Poisson -regressiolla, hieman yli 20 % DIPP-ravintotutkimuksen 3- ja 6-vuotiaista arvioitiin olevan todellisia maksamakkaran tai –pasteijan syöjiä ja noin 40 % todellisia maksalaatikon syöjiä. Maksamakkaran tai –pasteijan todelliseksi syöntitiheydeksi todellisten maksansyöjien keskuudessa arvioitiin joka neljäs tai viides päivä ja maksalaatikon joka toinen viikko. Nämä arviot osoittavat, että todellisten maksansyöjien osuus on hyvin todennäköisesti suurempi, mutta syöntitiheys pienempi kuin mitä voitiin suoraan kolmen päivän havainnoista arvioida.

Retinoidien kerta-annos- ja pitkäaikaissaanti

Retinoidien saanti maksaruoan kerta-annoksesta jäi alle turvatason 30 000 µg RE, mikä osoittaa sen, että yksittäiset annokset maksaruokia hyvin todennäköisesti eivät altista lapsia haitallisille tasoille retinoideja.

Sen sijaan maksan pitkäaikainen käyttö voi altistaa lapset suuremmille retinoidipitoisuuksille kuin mitä voidaan pitää turvallisena. Kun retinoidien saantia verrattiin saannin turvallisiin ylärajoihin (800 µg RE/päivä 1- ja 3-vuotiaat ja 1 100 µg RE/päivä 6-vuotiaat), 15 % yksivuotiaista, 34 % kolmevuotiaista ja 28 % kuusivuotiaista ylittivät suositellun ylärajan. Maksaa syömättömillä ei ollut vaaraa ylittää suurinta saantirajaa.

Syöntitiheyden vaikutus pitkäaikaiseen saantiin

Tämä riskinarviointi osoittaa, että maksaa syövillä lapsilla retinoidien saanti voi ylittää siedettävän ylärajan. Suurin riski liittyy maksakastikkeen ja –pihvien käyttöön. Seuraavina tulevat maksalaatikko sekä maksamakkara- ja pasteija. Maksaruokia voi kuitenkin sisällyttää 1–6-vuotiaiden ruokavalioon, kunhan niitä ei syödä liian usein. Annoskoon ohella syöntitiheys on keskeinen tekijä maksaruokien turvallisessa pitkäaikaiskäytössä.

Yleisesti maksamakkaraa tai –pasteijaa voi syödä useammin kuin pääruokana syötäviä maksaruokia (maksalaatikkoa, maksapihvejä tai maksakastiketta). Ikäryhmästä riippumatta (1-, 3- ja 6-vuotiaat) turvarajoja ei todennäköisesti ylitetä, jos maksamakkaraa tai –pasteijaa syödään kohtuullisina annoksina kerran viikossa. Samaan aikaan voidaan syödä vain yhtä maksapääruokaa, mutta harvemmin kuin maksamakkaraa tai –pasteijaa. Tällöin maksaa sisältävän pääruoan turvallinen syöntitiheys vaihtelee kuukaudesta kahteen kuukauteen riippuen ruuasta ja ikäryhmästä.

Summary

Vitamin A
Vitamin A is an essential, naturally occurring, fat-soluble nutrient that is involved in several important biological processes such as vision, cell growth and diversification, the defence mechanisms of the body, and foetal development. Both deficient and excessive intake of vitamin A may cause health problems. Vitamin A deficiency is rare in the Western world but the risk of excessive intake of vitamin A in retinoid form exists. On the other hand, overconsumption of carotenoids has not been shown to result in hypervitaminosis.

The body is not capable of producing vitamin A by itself which means that it has to be provided from the diet. In foods, vitamin A is derived from two sources: retinoids from foods of animal origin and provitamin A carotenoids mainly from plant-derived foods. Liver has higher retinoid content than any other food. Retinoids are also present in dietary fats, fatty milk products, fatty fish and eggs. Carotenoids are found in green leafy vegetables, yellow vegetables, and yellow and orange non-citrus fruits. In addition to foods, fortified foods and food supplements can contain vitamin A in the form of retinoids or carotenoids. Consuming natural sources of vitamin A rarely results in toxicity. The exception is toxicity resulting from excessively high intakes of liver or use of fortified foods and food supplements on a continued basis.

Project history and objectives
At the turn of 1989, very high concentrations of vitamin A (retinoids) in livers of pigs were reported in Finland (Heinonen 1990). Due to the possible risk of retinoids, pregnant women and children have been advised to restrict the consumption of liver-based foods since 1990. The vitamin A level in pig livers was, however, soon lowered by reducing the use of vitamin A in animal feeds and healthcare. Despite reduced retinoid content in livers, the recommendations on liver consumption for pregnant women and children remained unchanged.

A risk assessment on the exposure of Finnish women of fertile age to vitamin A from liver-based foods was completed by the Finnish Food Safety Authority in 2007 (Mavira –project; Lavikainen et al. 2007). Based on the risk assessment, the authorities made the decision to ease the recommendations concerning the consumption of liver. The risk assessment confirmed that during pregnancy the consumption of liver dishes as the main course should still be avoided. Moderate consumption of liver sausage or liver pâté is safe, however.

The objectives of this risk assessment were to estimate retinoid exposure from liver products among Finnish 1-, 3- and 6-year-old children and to assess whether the restriction of the consumption of liver-based foods by children is still necessary.

Exposure assessment
For estimating vitamin A and retinoid intake, consumption data of 963 one-year-olds, 835 three-year-olds and 850 six-year-olds were obtained from the Finnish Type I Diabetes Prediction and Prevention (DIPP) Nutrition Study. In addition, laboratory analyses of swine (n=91), bovine (n=76) and chicken (n=270) liver samples, and market shares and recipe information from the industry and the National Public Health Institute of Finland were used.

Based on the collected data, Monte Carlo simulation models were built to estimate children's vitamin A and retinoid intake whether liver foods are eaten or not. Results were compared with the intake recommendations for

vitamin A and with the intake limits for retinoids. The models were also applied to estimate safe portion sizes and eating frequency of liver foods.

Retinoids in liver foods

The estimated mean retinoid content was the highest in liver patties (82 µg RE/g, range 15-806 RE/g) followed in descending order by liver sauce (54 µg RE/g, range 12-474 RE/g), liver sausage or pâté (26 µg RE/g, range 8-59 µg RE/g) and liver casserole (15 µg RE/g, range 10-41 µg RE/g). The retinoid content varied within the liver food groups reflecting variation both in the retinoid content of the livers used as an ingredient and in the recipes (amount of liver) of liver foods.

Intake of vitamin A and retinoids among liver and non-liver eaters

About 1% of 1-year-olds and 18% of 3- and 6-year-olds had eaten liver foods during a 3-day food recording period. The most commonly eaten liver food was liver sausage or pâté followed by liver casserole. Only a few children ate liver sauce or liver patties.

The importance of liver as a vitamin A source was clear because among liver eaters, an average 54-57% of retinoid intake and 39-48% of total vitamin A intake came from liver foods. All liver eaters achieved the average vitamin A requirement of 210 µg RE/day for 1- and 3-year-olds and 275 µg RE/day for 6-years-olds whereas a whole 41% of 1-year-old and about 10% of 3- and 6-year-old non-liver eaters had an intake below the estimated average requirement.

True liver eaters

The weakness of the consumption data was that it didn't include information about the proportions of true liver and non-liver eaters. It is very likely that the real proportion of liver eaters among the study population was higher and part of responders just didn't happen to eat liver products during those 3 days they filled in the food record.

When eating frequency and proportion of true liver eaters were estimated by zero-inflated Poisson regression, slightly over 20% of 3- and 6-year-old DIPP Nutrition Study children were estimated to be true liver sausage or pâté eaters, and about 40% true liver casserole eaters. True eating frequencies were estimated to be every fourth or fifth day and every second week for liver sausage or pâté and liver casserole, respectively. These estimates indicate that in real populations the proportion of true liver eaters is very probably much higher, but eating frequency among true eaters is lower than could be estimated directly according to 3-day observations.

Single meal and long term intakes of retinoids

The amount of vitamin A obtained from liver-based retinoids, remained below the specified safe level of 30 000 µg RE from a single portion indicating that moderate single portions of liver foods probably do not expose children to harmful doses of retinoids.

Instead, long term liver consumption may expose children to retinoid intakes higher than what is considered safe. When the retinoid intake estimates were compared with upper tolerable daily intake levels for children (800 µg RE/day for 1- and 3-year-olds and 1 100 µg RE/day for 6-year-olds), 15%, 34% and 28% of 1-, 3- and 6-year-old liver eaters, respectively, exceeded the recommended upper intake limit. Among non-liver eaters, there was no risk of exceeding the maximum intake limit.

Effect of eating frequency on long term retinoid intake

This risk assessment indicated that among liver eaters, dietary retinoid intakes may exceed the tolerable upper levels for children. The highest risk is related to the consumption of liver sauce or patties followed in descending order by liver casserole and liver sausage or pâté. Liver foods can, however, be included in the diet of 1-6-year-old children as long as they are not eaten too often. In addition to portion size, eating frequency is an important factor in safe long term consumption of liver foods.

In general, liver sausage or pâté can be eaten more often than liver main courses (liver casserole, liver sauce and liver patties). Independent of age group (1-, 3- or 6-year-olds), safety thresholds are not likely to be exceeded if liver sausage or pâté is eaten in moderate amounts once a week. At the same time, only one of the liver main courses can be eaten but more seldom than liver sausage or pâté: the safe eating frequency varied from once a month to once every two months depending on the liver main course and age group.

Risk assessment

1. Introduction

1.1 Vitamin A

Vitamin A is an essential nutrient that plays a very important role in many biological processes. It can not be synthesised *de novo* within the body, and has to be provided from the diet. Vitamin A in foods is derived from two sources: retinoids from foods of animal origin and provitamin A carotenoids mainly from plant-derived foods. The retinoid content of liver is several times higher than in any other foodstuffs (KTL 2005). In addition to intake from foods, vitamin A can be taken as food supplements in the form of retinoids or carotenoids.

1.2 Project history

At the turn of 1989, very high concentrations of vitamin A in livers of pigs were reported in Finland (Heinonen 1990). Consequently the authorities gave recommendations to decrease the use of liver foods (Julkunen et al. 1990). By changing the composition of animal feeds and cutting down on the overuse of additional vitamin preparations, the vitamin A level in pig livers was soon lowered. Despite reduced vitamin A content in livers, the recommendations for liver consumption by pregnant women and children remained unchanged. In order to prevent excessive intake of vitamin A, liver-based foods have not been recommended since 1990 for children under the age of one year. For toddlers, it has been advised to restrict the consumption of liver-based foods (ground liver patties, liver steak, liver stew, and liver casserole), liver sausage and liver pâté to a couple of meals per month (Hasunen et al. 2004).

The Finnish Food Safety Authority published in August 2007 a risk assessment on the exposure of Finnish women of fertile age to vitamin A (Mavira –project; Lavikainen et al. 2007). Based on the risk assessment, the authorities eased the recommendations concerning the consumption of liver. The risk assessment confirmed that consumption of liver-based foods during pregnancy should still be restricted because the amount of vitamin A obtained from a liver-based meal may considerably exceed the safe intake limit from a single portion. Moderate consumption of liver sausage or liver pâté, however, will not result in the limit being exceeded.

This risk assessment started in September 2007 and is a continuation of the risk assessment of retinoid intake from liver foods among Finnish women of fertile age, and it evaluates whether the restriction of children's consumption of liver-based foods is still necessary.

1.3 Objectives

The objectives of this research were

1. To estimate retinoid intake from liver products among Finnish 1-, 3- and 6-year-old children.
2. To assess the risk of intolerably high retinoid intake if recommendations for consumption would be removed or whether they would be loosened.

1.4 Parts of risk assessment

This risk assessment follows the format of the Codex Alimentarius Commission (CAC 2004) and consists of four parts: hazard identification, hazard characterisation, exposure assessment and risk characterisation. They are described below:

1. **Hazard identification:** Describes the general properties of vitamin A, such as chemistry, sources and metabolism, bioavailability and physiological functions. Hazard identification includes the current intake recommendations.
2. **Hazard characterisation:** Describes the toxicological properties of vitamin A. The common symptoms occurring due to excessive or insufficient intakes are characterised. The toxicity to children is described, and recommended safety limits are discussed.
3. **Exposure assessment:** Evaluates the exposure to retinoids from liver foods among Finnish 1-, 3- and 6-year-old children. This part consists of two subsections: 1) The consumption of food products containing liver is estimated based on data obtained from the DIPP Nutrition Study and 2) The intake of retinoids from liver products is then estimated by using a simulation model constructed for this study. Recipes of liver foods and retinoid contents of livers are obtained from the MAVIRA-project. As the importing of liver into Finland is very marginal, it is not included in the assessment.
4. **Risk characterisation:** This step brings together the preceding three sections. The effects of liver consumption on intake of total vitamin A and retinoids are studied. Results are compared with the intake recommendations and safety levels for children. The models are also applied to estimate safe combinations of portion size and eating frequency for liver foods and their combinations.

2. Hazard identification of vitamin A

2.1 Chemical structure and definitions

Vitamin A is the generic name for retinoids (retinol, retinyl, retinal and retinoic acid) and carotenoids which have retinol (IUPAC-IUB 1981) activity. It is an essential nutrient that plays a very important role in a large number of physiological functions.

Generally, the structure of retinoids consists of a six-carbon β-ionone ring, a conjugated isoprenoid side chain, and a polar terminal group with an oxidation state that may vary: a hydroxyl group in retinols, an aldehyde in retinals, and a carboxylic moiety in retinoic acids (Figure 1). Differences in the functional group and alterations in the molecular skeleton give about 600 different retinoid analogues with different chemical properties and potentially different biological activities (Gundersen & Blomhoff 2001).

The term vitamin A includes retinol and provitamin carotenoids that are dietary precursors of vitamin A and can be converted to retinol in the body. Provitamin A carotenoids are less biologically active than retinol. They are derived from a 40-carbon polyene chain, which is terminated by one or two cyclic end-products (Sklan 1987) (Figure 2). About 50 of the 600 carotenoids found in nature, can be converted into retinol. Carotenoids with provitamin A activity are β-carotene, α-carotene, γ-carotene and β-cryptoxanthin. β-Carotene is the most important of the provitamin carotenoids in terms of its relative provitamin A activity and quantitative contribution to the diet (Underwood 1984; Bendich & Langseth 1989).

The vitamin A activity is expressed in terms of 'retinol equivalent' (RE), where

1 µg RE = 1 µg retinol = 1.78 µg retinyl palmitate = 12 µg β-carotene = 24 µg other carotenoids with provitamin A activity = 3.33 IU vitamin A activity from retinol (FNB 2001; EVM 2003).

In this assessment, the term vitamin A refers to the total amount of vitamin present in the diet, including retinoids and provitamin A carotenoids. The term retinoids is used to group retinol and its natural and synthetic derivatives that have the biological activity of retinol.

2.2 Dietary sources

Vitamin A cannot be synthesised *de novo* by the human body, and has to be provided from the diet. Vitamin A is found naturally in many foods (Table 1). It occurs mainly as retinoids in foods of animal origin and in the form of provitamin A carotenoids in plant foods. In addition to foods, fortified foods and food supplements can contain vitamin A in the form of retinoids or carotenoids.

Liver has a higher retinoid content than any other food. Retinoids are also present in dietary fats, fatty milk products, fatty fish and eggs. Carotenoids are found in green leafy vegetables, yellow vegetables, and yellow and orange non-citrus fruits (Booth et al. 1992).

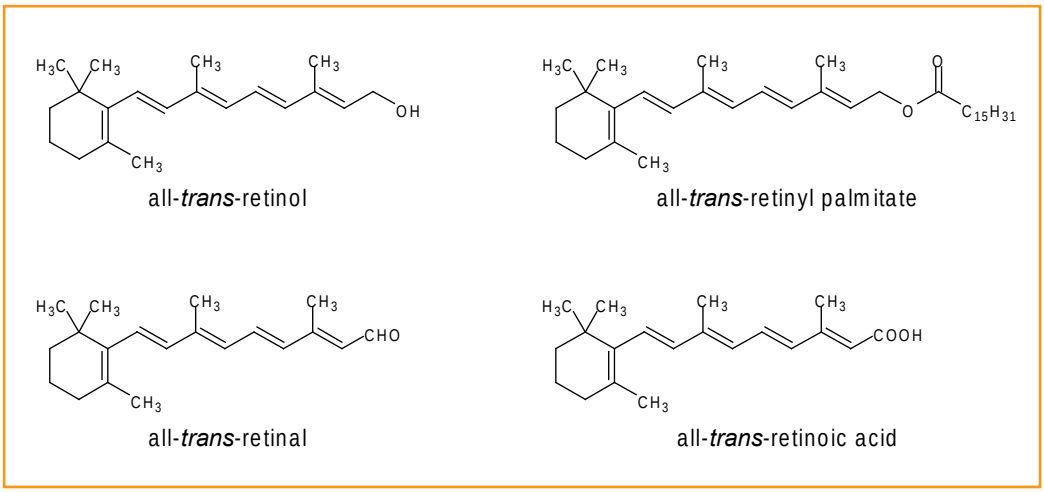

Figure 1. *Chemical structures of some natural retinoids.*

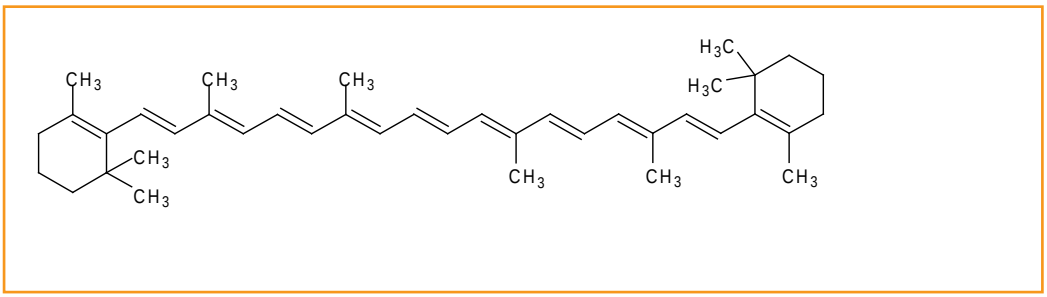

Figure 2. *Chemical structure of β-carotene*

Table 1. Mean vitamin A content of some Finnish foods (KTL 2005).

Food	Mean vitamin A content (µg RE/ 100 g)	Food	Mean vitamin A content (µg RE/ 100 g)
In retinoid form		In carotenoid form	
Liver (average)	18 000	Rose hip puree	1 230
Margarine, fat spread	850	Carrot	774
Butter	706	Sweet potato	767
Fatty fish (average)	648	Borecole	766
Infant formula	519	Pumpkin	367
Cream, fatty	334	Spinach	275
Egg	260	Red paprika	243
Cheese (average)	231	Celery	243
Fish (average)	67	Broccoli	85
Beef burger (pig-bovine)	61	Leek	83
Chicken	37	Lettuce	82
Beef steak	5	Tomato	66
		Pea	31
		Orange	10

2.3 Metabolism

2.3.1 Absorption

In foods, retinoids occur mainly as retinyl esters. After ingestion, retinyl esters are completely hydrolysed in the intestinal lumen (Harrison 2005). Free retinol is then taken up by intestinal cells, bound to a specific cellular retinol-binding protein (RBP) and re-esterified with long chain, mainly saturated, fatty acids. The resulting retinyl esters are incorporated with other neutral lipid esters into large lipoproteins called Chylomicrons.

Provitamin A carotenoids are either cleaved to generate retinol or are absorbed intact. In the former case, that is the major pathway, the molecules are cleaved centrally to two molecules of retinal, converted to retinyl esters and then transported to the liver as described above. Some intact carotenoids can also be transported to the peripheral tissues via Chylomicrons. In peripheral tissues, they can be further transformed into retinoids (Perrotta et al 2003; Debier & Larondelle 2005; Harrison 2005). The conversion of β-carotene to retinol is regulated so that excess retinol is not absorbed from carotene sources (Underwood 1985; Bendich & Langseth 1989)

2.3.2 Storage and blood transport

Chylomicrons containing newly absorbed retinyl esters are released into the blood circulation via the lymph, and Chylomicron remnants are formed in blood capillaries. Most of the retinyl esters in the Chylomicrons remnants are taken up by the liver. In liver parenchymal cells, retinyl esters are rapidly re-hydrolysed to retinol. Free retinol binds to a specific transport protein, RBP. Retinol bound to RBP (holo-RBP) can be secreted directly into the circulation or transferred to the stellate (fat storing) cells and stored in the form of long-chain fatty esters (Debier & Larondelle 2005; Harrison 2005).

About 90% of the total body vitamin A reserves are stored in the liver, within the adipose tissue, extrahepatic stellate cells in lungs, kidneys and intestine as minor sites (Tsutsumi et al. 1992; Olson 1996; Nagy et al. 1997). Unlike retinoids, carotenoids are deposited mainly in adipose tissues and relatively small amounts are stored in the liver (Goodman 1984; Olson 1984).

When needed, stored retinol is transferred back to parenchymal cells and released into the circulation as holo-RBP. Homeostatic mechanisms regulate mobilization and release of holo-RBP ensuring that plasma retinol concentrations remain constant, the range under normal conditions being 1-3 µmol/L (Underwood 1979; Olson 1996 & 2001; Thurnham & Northrop-Clewes 1999; Penniston & Tanumihardjo 2006).

2.3.3 Tissue uptake

Retinol is believed to enter the target cells mainly as holo-RBP. Depending on tissue type, retinol is either transformed into retinyl ester and stored in lipid droplets (adipose tissue) or activated into retinoic acid or retinal (eyes, lungs) (Debier & Larondelle 2005).

2.4 Bioavailability

Under normal physiological conditions about 70-90% of ingested preformed vitamin A is absorbed. The absorption efficiency of provitamin A carotenoids is much lower, ranging from 5% to 50% (Blomhoff et al. 1991; Garrow et al. 2000). The absorption is influenced by a number of factors including type and amount of the vitamin A source consumed, food matrix, food processing, the fat content of the accompanying meal (Ribaya-Mercado 2002). Oil solutions of carotenoids seem to be more bioavailable than those from food matrices, and heating can improve the bioavailability of carotenoids from some food products (Parker et al. 1999, van Lieshout 2001; Ribaya-Mercado et al. 2007).

2.5 Biological functions

Vitamin A is an essential nutrient for all animal species because of its critical role in vision, gene expression, reproduction, embryonic development, growth, and immune function (Perrotta et al. 2003; Villamor & Fawzi 2005). These roles are particularly critical during periods of proliferative growth and tissue development, as in pregnancy, infancy, and early childhood (Underwood 1994a, b).

The main active form of vitamin A is retinoic acid. Cellular retinoic acid can be obtained from either the conversion of retinol to retinal and then to retinoic acid or direct uptake from blood circulation. The two biologically active isomers of retinoic acid are all-*trans*-retinoic acid and its 9-*cis* isomer. Retinoic acids act as regulators of genomic expression and are considered to be responsible for all the functions attributed to vitamin A, with the exception of vision. Retinoids regulate not only transcription via the activation of specific retinoid receptors. They can also form a covalent bond with some proteins, which can modify the properties of the target protein and thus its activity (Gerster 1997; Marill et al. 2003; Debier & Larondelle 2005).

The active form of vitamin A in vision is retinal, which is derived from circulating retinol and retinyl esters. Retinal is essential for vision in darkness as well as for colour perception. It is situated in the photoreceptors of the retina. Two types of photoreceptors are present in the retina: rhodopsins and iodopsins. The former are situated in the rods and are involved in vision in dim light. The latter are present in cones and are involved in colour perception and vision in bright light (Olson 1984; Debier & Larondelle 2005).

2.6 Vitamin A intake

2.6.1 Requirement and recommended intake

The recommended dietary intake (RDI), a term used worldwide, or recommended dietary allowances (RDA), a term used in the United States (US) and in a few other countries, is defined as the daily nutrient intake level that would theoretically meet the needs of nearly all healthy individuals in a particular life stage and gender group. A RDI or RDA is calculated from the nutrient's estimated average requirement (EAR) which is the daily nutrient intake level that fulfils the average physiological requirements of a specified group. RDI or RDA is set at a level generously above the EAR but significantly lower than the level where toxicological data indicates any adverse effects (FNB 2001; NCM 2004).

The RDI or RDA for vitamin A is based on estimated requirements that ensure body stores of retinol where no clinical signs of deficiency are observed, adequate plasma retinol levels are maintained and there is protection against vitamin A deficiency for approximately 4 months on a vitamin A-deficient diet (NCM 2004).

Most countries recommend between 500 and 900 µg retinol equivalents (RE) for adults per day (NCM 2003). Finnish recommendations (VRN 2005) for vitamin A intake for adults are equal to Nordic (NCM 2004) and US recommendations (FNB 2001). EAR is 600 and 500 µg/d and RDI 900 and 700 µg/d for men and women, respectively.

Extrapolating data from adults to children and adolescents

For infants aged 0 to 12 months, adequate vitamin A intake can be determined by estimating the intake from human milk. Data is not available to estimate EAR for children aged 1 year and older and adolescents. Therefore, the EAR for children and adolescents has been extrapolated from those for adults by using metabolic body weight ($kg^{0.75}$) and growth factors (FNB 2001; NCM 2004).

The extrapolation method assumes that 1) Maintenance needs for vitamin A, expressed with respect to metabolic body weight [(kilogram of body weight)$^{0.75}$], are the same for adults and children, 2) The EAR for adults is an estimate of maintenance needs, 3) The proportion of extra vitamin A needed for growth is similar to the proportion of extra protein needed for growth and is used as an estimate of the growth factor, 4) On average, total needs do not differ substantially for males and females until age 14, when reference weights differ (FNB 2001).

The formula used for the extrapolation (FNB 2001) is

$$EAR_{child} = EAR_{adult} \times [(weight_{child}/weight_{adult})^{0.75} \times (1 + \text{growth factor})]$$

where $weight_{child}$ and $weight_{adult}$ are reference weights and
where the average proportional increase in protein requirement for growth is used as an estimate of the growth factor. Reference weights and growth factors used by the US Institute of Medicine (FNB 2001) are shown in table 2.

Table 2. Reference weights and growth factors for children and adults in the US (FNB 2001)

Gender	Age	Reference weight (kg)	Growth factor
Male, female	2-6 mo	7	
	7-11 mo	9	0.3
	1-3 y	13	0.3
	4-8 y	22	0.15
Male	9-13 y	40	0.15
	14-18 y	64	0.15
	19-30 y	76	
Female	9-13 y	40	0.15
	14-18 y	57	0
	19-30 y	61	

Recommendations for infants, children and adolescents

Finnish recommendations for vitamin A intake for children and adolescents (Table 3; VRN 2005) are equal to Nordic recommendations (NCM 2004), i.e. 300-600 µg RE/day, which are primarily based on assumptions and calculation methods used for United States reference subjects (FBN 2001). An adequate intake (AI) for infants (0-6 mo: 400 µg RE/day, 7-12 mo: 500 µg RE/day) used in the USA reflects a calculated mean vitamin A intake of infants principally fed human milk (FNB 2001). In Nordic countries, specific recommended intake of vitamin A for infants aged 0-6 months has not been given, because breast milk from well-nourished mothers usually contains sufficient amounts of vitamin A and vitamin A content of formula is sufficient for non-breast fed infants (NCM 2004).

The recommendations of FAO/WHO differ slightly from those of Nordic and US recommendations. This is due to different definitions of dietary reference intakes for vitamin A. The FAO/WHO defines the "mean requirement" for vitamin A as the minimum daily intake to prevent xerophthalmia in the absence of clinical or sub-clinical infection. The recommended safe intake is defined as the average continuing intake of vitamin A required to permit adequate growth and other vitamin A-dependent functions and to maintain an acceptable total body reserve of the vitamin (FAO/WHO 2002).

In order to prevent excessive intake of vitamin A, liver-based foods are not recommended for children under the age of one year in Finland. For toddlers, the consumption of liver-based foods (ground liver patties, liver steak, liver stew, liver casserole), liver sausage and liver pâté have been advised to be restricted to a couple of meals per month. The recommendations date back to the beginning of the1990s.

2.6.2 Current intake

Based on the results of a Finnish STRIP-study in 1995, on average Finnish children receive an adequate amount of vitamin A from food. Compared to the dietary recommendations, the intake of vitamin A from the diet of Finnish children is even more than adequate (Table 4). In the USA, the mean vitamin A intakes are also well above the recommended levels in all age groups (NHANES survey in 1999-2000; Ervin et al. 2004). For children aged 1-3 y, the median vitamin intake from food was 484 µg of retinol activity equivalent/d (RAE/d), and the 95th percentile was 1259 µg of RAE/d. The median intake from supplements was 721 µg of RAE/d, and the 95th percentile was 1482 µg of RAE/d. There is no evidence however, that these levels of intake would have caused toxicity in the United States (FNB 2001; Allen & Haskell 2002).

Table 3. Vitamin A intake recommendations for infants, children and adolescents (µg RE/day).

Source/age group	Estimated average requirement (EAR)	Recommended daily intake (RDI)
Finland (VRN 2005)		
6-11 mo		300
12-23 mo		300
2-5 y		350
6-9 y		400
10-13 y		600
14-17 y		
male		900
female		700
USA (FNB 2001)		
1-3 y	210	300
4-8 y	275	400
9-13 y		
male	445	600
female	420	600
14-18		
male	630	900
female	485	700
FAO/WHO[1] (2000)		
0-6 mo	180	375
7-12 mo	190	400
1-3 y	200	400
4-6 y	200	450
7 y	250	500
10-18 y	330-400	600

[1]Mean requirement and recommended safe intake.

Table 4. Vitamin A intake among children in the Turku area (Finnish STRIP-study, 1995 in Hasunen et al. 2004).

Age	Average intake µg RE/day
13 mo	717
2 y	665
3 y	776
4 y	880
5 y	875
6 y	836

3. Hazard characterisation of vitamin A

3.1 Vitamin A deficiency

Vitamin A deficiency (VAD) is rare in the Western world, but is a leading cause of growth failure, morbidity, mortality, and blindness in developing countries. It can occur in individuals of any age. However, it is a disabling and potentially fatal public health problem in developing countries for children under 6 years of age (FAO/WHO 2002; Underwood 2004).

The first specific symptom associated with VAD include visual problems such as night blindness and xerophthalmia (xero = dry, ophthalm = eye) that may end in irreversible blindness. VAD-dependent blindness is most prevalent in children under 3 years of age. It's also well known that VAD causes immunodeficiency, which may occur among children as respiratory and digestive tract infections (Cser et al. 2004). It also results in anaemia regardless of the iron status of the body (West 2003). There is also consistent evidence that an increased intake of vitamin A in developing countries, achieved by supplementation or food fortification, can improve the survival of infants and young children (Villamor & Fawzi 2000; McLaren & Frigg 2001; D´Souza & D´Souza 2002; West 2002; Benn et al. 2003; Benn et al. 2005).

There are three main causes of vitamin A deficiency in young children. Their mothers might be deficient and produce breast milk low in vitamin A or they are weaned onto diets that provide too little vitamin A. A third contributing factor is that children in developing countries are so often ill, that anorexia, malabsorption and increased catabolism further deteriorate their vitamin status (Miller et al. 2002). In addition, plant foods containing provitamin A carotenoids often are the primary sources of vitamin A in some populations. Thus, strategies for improving the absorption and bioconversion of plant carotenoids are essential (Oso et al. 2003; Ribaya-Mercado et al. 2007).

3.2 Retinoid toxicity

3.2.1 Hypervitaminosis A

Retinoids are fat soluble and readily accumulate in the liver. Their absorption is rapid and clearance slow. As a result, excess intake of retinoids can result in hypervitaminosis A among children and adults or teratogenicity during the foetal stage (Hathcock 2004). Consuming natural sources of vitamin A rarely result in toxicity. The exception is toxicity resulting from excessively high intakes of liver or use of food supplements on a continued basis.

Toxicity appears to occur only when the amount of retinoids present exceeds the capacity of retinol binding proteins (RBP) to bind to them. Retinoids that are not bound to RBP bind to lipoproteins, and in this form they have toxic effects. In other words, in vitamin A toxicity, plasma RBP levels are normal but concentrations of retinoids not bound to the specific RBP are increased (Smith and Goodman 1976; Perrotta et al. 2003). Overconsumption of carotenoids has not been shown to result in hypervitaminosis A, presumably because its cleavage to retinoids is tightly regulated (Bendich 1988; Dawson 2000).

Vitamin A toxicity in humans may be generally categorized as either acute or chronic. Acute

toxicity occurs within hours or at most a day or two after a very large intake. Chronic toxicity occurs when lesser amounts that are not acutely toxic are consumed for several weeks, months, or years. Biological indicators of toxicity include high serum retinol concentrations, production of toxic metabolites, high vitamin A concentrations in the liver and liver damage (Allen & Haskell 2002).

In general, acute toxicity is less of a problem than is chronic toxicity from preformed vitamin A (Olson 2001; Penniston and Tanumihardjo 2006). Acute cases are, however, mostly reported among small children 0-2 years old, whereas chronic hypervitaminosis is more common in older age groups (Myhre et al. 2003).

3.2.2 Symptoms

The pattern of adverse symptoms varies with the dose and the duration of exposure as well as with the age of the individual exposed. Myhre et al. (2003) performed a meta-analysis of case reports on toxicity claimed to be induced by intakes of excessive amounts of retinol and retinyl esters in foods or supplements. Table 5 shows symptoms registered in cases with acute or chronic hypervitaminosis A. Of the 259 cases registered, 55 were acute and 204 chronic. Of those reporting the source of retinol, 4, 24, 36, and 32 cases came from ingestion of retinol in liver, oil, emulsified and water-miscible solutions, and solid tablets, respectively. Almost all of the subjects with acute hypervitaminosis (50 cases) were in the age group 0-2 years. Most of these acute cases experienced symptoms of the nervous, visual, and gastrointestinal systems. Over one third of the group reported general symptoms of a deteriorating state of health (e.g. fever, loss of appetite, and fatigue). For the age groups 0-2 years (n=50) and 3-16 years (n=39), symptoms of the skin, visual, nervous system, gastrointestinal system, and musculoskeletal system, and general symptoms of a deteriorating state of health were reported in over 50% of the chronic cases.

Table 5. Symptoms registered in cases with acute or chronic hypervitaminosis A among children aged 0-16 years (Gamble & Ip 1985; Hathcock et al. 1990; Myhre et al. 2003).

Nervous system and vision	Bulging of fontanel, Headache, Cerebral irritability, Papillary edema, Hydrocephalus, Increased CSF pressure, Diplopia, Pseudotumour cerebri, Ataxia, Blurred vision, Disturbance of consciousness
Gastrointestinal system	Vomiting, Nausea, Abdominal pain, Hepatomegaly, Splenomegaly
Vascular system	Edema: head, leg or ankle, abdomen
Musculoskeletal system	Hyperostosis, Skeletal pain, Muscular stiffness and pain, Joint pain
Skin and hair	Lip fissure, Alopecia, Pigmentation, Dryness, Desquamation, Pruritus, Pale, Haemorrhage, Exanthema
Urogenital system	Menstrual change
Symptoms of deteriorating state of health	Loss of appetite, Fatigue, Tiredness, Fever, Impaired immunity, Weight loss, Sleep disturbance

3.2.3 Dose response

Intake of retinol in various physical forms appears to have different thresholds for toxicity. Retinol in water-soluble, emulsified or solid preparations generally seems to have more acute toxic effects than retinol in foods or oils (Myhre et al. 2003). It is known from a series of studies that retinol is absorbed much better from emulsified than oily solutions (NCM 2003).

Acute toxicity

According to Olson (2001), acute toxicity in children may even begin with doses of > 20 x the RDA for vitamin A. For 1-3-year-old children this would mean doses of > 460 µg RE/kg. In adults, doses > 100 x RDA may cause acute toxicity. In the meta-analysis carried out by Myhre et al. (2003) using 259 hypervitaminosis A cases, acute toxicity was seen with supplemental doses of 3 500- 29 200 and 8 000-16 700 µg RE/kg body weight in children aged 0-2 (n=50) and 3-16 (n=3) years, respectively. They concluded that the safe upper single dose of retinol in oil or liver for infants and small children is ~ 3 000-3 500 µg RE/kg body weight, whereas water-miscible and emulsified forms of retinol have a lower threshold. For adults, the safe upper single dose of retinol in oil or liver is ~ 4 000-6 000 µg RE/kg body weight (Myhre et al. 2003). Table 6 shows tentative cut-off levels proposed by Allen & Haskell (2002). They are levels in the diet or in body tissues that indicate there may be some risk of toxicity.

Chronic toxicity

Onset of chronic toxicity is dependent on the dose and the length of exposure. According to Olson (1987), toxic doses are at least 10 times higher than the RDA (1-3 year olds: > 230 µg RE/kg body weight) and usually cannot be obtained from foods except by the chronic ingestion of significant amounts of liver. For children, daily intakes of 450 µg/kg body weight have reportedly led to toxicity (Bendich et al. 1989; Hathcock et al. 1990; Coghlan & Cranswick 2001; Penniston and Tanumihardjo 2006). In the meta-analysis of Myhre et al. (2003), chronic toxicity was reported with daily doses of 190-18 800 and 70-4600 µg RE/kg body weight in children aged 0-2 (n=50) and 3-16 (n=39) years, respectively. Chronic hypervitaminosis was concluded to be induced after daily doses of 2 000 µg RE/kg in oil-based preparations for many months or years (Myhre 2003). In contrast, doses as low as 200 µg RE/kg in emulsified/water-miscible and solid preparations for only a few weeks seemed to cause chronic hypervitaminosis A (Myhre et al. 2003).

Tolerance to excess vitamin A intake has also been seen to vary between individuals. In one case study, two boys were given chicken liver that supplied about 690 µg/day vitamin A and various supplements that supplied another 135 to 750 µg/day. One boy developed toxicity symptoms at the age of 2 years, and the other one at the age of 6 years. An older sister who had been treated similarly remained completely healthy (Carpenter et al. 1978; FNB 2001).

Table 6. Cut-off levels for vitamin A toxicity in the diet or in body tissues (µg/d) (Modified from Allen & Haskell 2002).

Outcome	Group	Intake	Concentration
Acute toxicity symptoms	Infant 0-6 months	15 000 µg dose (2 100 µg/kg)[1]	
	Infant 7-11 months	> 30 000 µg dose (3 300 µg/kg)[1]	
	Child > 12 months	30 000 – 60 000 µg dose (3 300 – 4 600 µg/kg)[1]	
Liver damage/chronic toxicity symptoms	Infants/children	> 1 000 µg /d, long term (140 µg/kg/d)[1]	
Excessive liver accumulation	Women and children		300 µg/g
High serum retinol	Women and children		> 100 µg/dL

[1]Intake/kg body weight calculated by using following reference weights (FBN 2001):
2-6 mo 7 kg, 7-11 mo 9 kg, 1-3 y 13 kg

3.2.4 Tolerable upper levels

The tolerable upper level (UL) is defined as the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects for almost all individuals in the general population. As intake increases above the UL, the risk of adverse effects increases. If possible the UL is derived from the no observed adverse effect level (NOAEL), which is the highest intake at which no adverse effects have been reported or from the lowest observed adverse effect level (LOAEL), which is the lowest intake at which an adverse effect has been identified. The UL is several-fold lower than the NOAEL or LOAEL, and it is derived by dividing the NOAEL (or LOAEL) by a single uncertainty factor that incorporates all relevant uncertainties.

The Institute of Medicine in the USA (FNB 2001; Allen & Haskell 2002) and the Scientific Committee on Food (SCF) in the EU (SCF 2002) have recommended ULs for vitamin A intake (Table 7). Because, there is more data on which to base the NOAEL for infants than there are for children over 12 months of age, the UL values for children and adolescents have been extrapolated from the value of 3000 µg RE/d for adults. The US Institute of Medicine uses reference body weights in the extrapolation, when the formula is

$$UL_{child} = UL_{adult} \times Weight_{child}/Weight_{adult}$$

where
UL_{child} is extrapolated UL-value of specific child age group
UL_{adult} is the value for adults; 3000 µg RE/d
$Weight_{child}$ and $Weight_{adult}$ are reference body weights for children and adults (Table 3).

The extrapolation used by SCF is also based on the value of 3000 µg RE/d for adults but the correction for differences in basal metabolic rate compared to adults uses scaling according to body surface area (body weight$^{0.75}$), which gives slightly higher UL-values than the use of the simple ratio of body weights. Thus, the formula is

$$UL_{child} = UL_{adult} \times (Weight_{child}/Weight_{adult})^{0.75}$$

Table 7 shows the UL values for preformed vitamin A intake of children and adolescents. When compared to recommended intakes above in Table 3, it can be seen that the ULs are 2-3 times higher than recommended daily intakes.

Table 7. Tolerable upper level (UL) for preformed vitamin A (retinol and retinyl esters; µg RE/d) (FBN 2001; Allen & Haskell 2002; SCF 2002).

	UL	
Age years	**Institute of Medicine, USA**	**SCF**
< 1	600[1]	
1-3	600[2]	800[2]
4-8	900[2]	
4-6		1100[2]
7-10		1500[2]
9-13	1700[2]	
11-14		2000[2]
14-18	2800[1]	
15-17		2600[2]

[1] Derived from the NOAEL or LOAEL
[2] Extrapolated from the value of 3000 µg RE/d for adults

4. Exposure assessment

4.1 Data sources

For exposure assessment, the following data sources were used:

1. The consumption of liver products among 1-, 3- and 6-year old Finnish children was obtained from the Finnish Type I Diabetes Prediction and Prevention (DIPP) Nutrition Study (Kupila et al., 2001, Virtanen et al. 2006).

2. Laboratory analyses of swine, bovine and chicken liver samples, carried out to obtain information on retinoid content in the raw material of liver foods, were obtained from the previous MAVIRA-project (Lavikainen et al. 2007).

3. The amount and type of liver in the consumed liver foods were estimated relative to the market shares of all Finnish liver products. The market shares and recipe information were obtained from the industry and the National Public Health Institute of Finland.

4. Data of retinoid and vitamin A intake from non-liver sources was also obtained from the DIPP Nutrition Study.

Based on the collected data, Monte Carlo simulation models were built to estimate children's vitamin A and retinoid intake whether liver foods are eaten or not. Results were compared with the intake recommendations for vitamin A and with the intake limits for retinoids. The models were also applied to estimate safe portion sizes and eating frequencies of liver foods.

4.1.1 DIPP Nutrition Study design

Data on consumption of liver products and intake of retinoids and vitamin A from non-liver foods and food supplements was obtained from the DIPP Nutrition Study. The data is from the years 2003-2006.

The DIPP study was established to predict type 1 diabetes and to develop effective strategies to prevent or delay progression of β-cell destruction to clinical disease in Finland (Kupila et al., 2001). The DIPP study was carried out in the University Hospital areas of Turku, Tampere and Oulu. Families with a newborn baby with genetic susceptibility for type 1 diabetes were invited to take part in the study.

Food consumption data were obtained from the DIPP Nutrition Study in the cities of Tampere and Oulu. The DIPP Nutrition Study aimed at characterizing prenatal and postnatal nutritional factors that relate to natural progression from genetic disease susceptibility to development of β-cell autoimmunity and further clinical type 1 diabetes. The parents and other caregivers (e.g. staff at day-care centres) recorded the child's food consumption using 3-day food records that included one weekend day. The families and day-care personnel received oral and written instructions to record with household measures (e.g. spoons, cups, glasses, pieces and decilitres) all the foods the child had eaten. Parents and day-care personnel also recorded the type, brand and preparation method of the foods used. The vitamin and mineral supplements used were recorded with their brand names and amounts as tablets, drops, spoonfuls or millilitres. A research nurse reviewed the records item by

item for completeness and accuracy, during the respective study visit after each recording period. When needed, missing data (e.g. portion sizes, food descriptions and food preparation methods) were added after a discussion with the mother or father. The research nurses and physicians received continuous education (from the research nutritionist) in order to be able to advise the parents to fill in the child's food records and to check the forms for possible contradictions and omissions.

The food consumption data was analyzed using an in-house software program developed by the National Public Health Institute (Ovaskainen et al., 1996). Nutrient values of the food composition database are mainly derived from chemical analyses of Finnish foods and are continuously updated by complementary data obtained from the Finnish food industry and international food composition tables. The database currently includes about 3000 individual food items and mixed dishes and more than 200 nutrients and other dietary factors. The system also allows creation or modification of specific recipes, which were used when appropriate. Standard recipes in the database are based on current Finnish cook books. Nutritional information of those food supplements registered as drugs in Finland were obtained from the Finnish pharmacopoeia. Information on food supplements other than drugs was obtained from the National Food Administration and the manufacturers.

4.2 Reported consumption of liver

In total, 12 (1.2%) of 963 one-year-old children, 150 (18.0%) of 835 three-year-old children and 155 (18.2%) of 850 six-year-old children reported liver consumption. All 1-year-old liver consumers ate only one liver food during the 3-day study period whereas 7 to 8% of 3- and 6-year-old liver consumers ate two liver foods during the study period. The most commonly eaten liver food was liver sausage or pâté followed by liver casserole. No 1-year-old and only few 3- and 6-year-olds ate liver sauce or liver patties (Table 8).

4.2.1 Reported eating frequencies

Eating frequency was defined as the number of study days when certain liver foods were eaten. All 1-year-old liver consumers ate liver foods only on one day during the 3-day study period whereas some 3- and 6-year old liver consumers ate liver sausage or pâté on all three days and liver casserole on two days. Eating frequencies are expressed in Table 9.

4.2.2 Reported portion sizes

Portion size was defined as the amount of liver food consumed during a day (g/day). Portion sizes are expressed in Table 10. The range of portions sizes for liver sausage or pâté and liver casserole varied between age groups and variation occurred also within each age group. However, the mean and median portion sizes of liver sausage or pâté were very similar between all age groups, whereas those of liver casserole increased with increasing age. The number of both liver sauce and liver patty portions was low and gave only some references of relevant portion sizes.

Table 8. Reported use of different liver foods among 1-, 3- and 6-year-old children during the 3-day period in the DIPP Nutrition Study (1-year-olds: n = 963, 3-year-olds: n = 835, 6-year-olds: n = 850).

Age/Liver food	Number of consumers	Proportion of consumers (%)	
		Among liver consumers	Among all children
1 year			
Liver sausage or pâté	6	50	0.6
Liver casserole	6	50	0.6
Liver sauce	0	-	-
Liver patties	0	-	-
3 years			
Liver sausage or pâté	92	61.3	11.0
Liver casserole	66	44.0	7.9
Liver sauce	1	0.7	0.1
Liver patties	3	2.0	0.4
6 years			
Liver sausage or pâté	92	59.4	10.8
Liver casserole	68	43.9	8.0
Liver sauce	6	3.9	0.7
Liver patties	1	0.6	0.1

Table 9. Reported number of days when liver foods were eaten among 1-, 3- and 6-year-old children in the DIPP Nutrition Study.

Age/Liver food	Number of eating days during 3-day study			
	0	1	2	3
1 year				
Liver sausage or pâté	957	6	0	0
Liver casserole	957	6	0	0
3 years				
Liver sausage or pâté	743	65	23	4
Liver casserole	769	58	8	0
Liver sauce	834	1	0	0
Liver patties	832	2	1	0
6 years				
Liver sausage or pâté	758	64	19	9
Liver casserole	782	61	7	0
Liver sauce	844	6	0	0
Liver patties	849	1	0	0

Table 10. Reported portion sizes of liver foods among 1-, 3- and 6-year-old children in the DIPP Nutrition Study.

Age/Liver food	Number of portions	Portion size (g)		
		Mean	Median	Range
1 year				
Liver sausage or pâté	6	17	15	5-30
Liver casserole	6	77	48	5-180
Liver sauce	0	-	-	-
Liver patties	0	-	-	-
3 years				
Liver sausage or pâté	123	20	15	2-70
Liver casserole	74	117	100	5-300
Liver sauce	1	100	-	-
Liver patties	4	40	40	30-50
6 years				
Liver sausage or pâté	129	20	15	2-80
Liver casserole	75	151	150	10-450
Liver sauce	6	96	100	50-150
Liver patties	1	30	-	-

4.3 Production of liver foods

4.3.1 Liver in liver foods

To quantify the liver content of consumed liver foods, recipe information was used. For commercially available prepared liver foods (liver casserole and liver sausage and pâté), recipes were obtained from the Finnish food industry. For liver patties and liver sauce, which were not available as prepared food, the customary recipes of the National Public Health Institute of Finland were used. Information was gathered on both the amount and the type of liver (animal species). The amount of liver was reported as a percentage of the weight of the end product, i.e., the amount of raw liver (g) needed to produce 100 g of end product. Thus, the water loss during food manufacture was included in the numbers.

Finnish liver food manufacturers supplied the recipes of prepared liver foods. Reported liver contents were then weighted relative to the market shares in year 2004. The results are summarised in Table 11. Information was received on all but three products with a small market share (0.3-0.9%). In liver sausage and pâté, pork liver was the main ingredient, whereas in liver casserole several liver types are mixed and used in very variable proportions. Although the type of liver used may vary, the total liver content of the products is kept very constant by each manufacturer. The mean liver content in liver sausage or pâté was 20.5% (range 8-42%) and in liver casserole 13.6% (range 10-21%) (Table 11).

For liver patties and liver sauce, the following common recipes were obtained from the National Public Health Institute of Finland:

- liver patties: liver content 50%; one-third swine liver and two-thirds bovine liver.
- liver sauce: liver content 33%; one-third swine liver and two-thirds bovine liver.

In the recipes, swine liver includes both finishing pig liver and sow liver. According to Finnish food manufacturers, sow livers, however, make up no more than 10% of the swine livers used. Because the risk assessment of Lavikainen et al. (2007) showed that exclusion of sow livers from food production would have only a minor effect on retinoid intakes from liver foods, higher retinoid contents of sow livers were not taken into account but in the calculations all swine liver was supposed to be the finishing pig liver.

Table 11. Liver content of Finnish industrial liver foods obtained from food manufacturers. Contents are calculated as an arithmetic mean and as a weighted mean relative to market share. N = number of trade names with content information available/number of trade names on sale in 2004 (Lavikainen et al. 2007).

Product and statistics	Total liver content (%)[1]	Type of liver (% of total liver content)		
		Pig	Bovine	Chicken
Liver sausage and pâté (n=24/27)				
• Mean (min-max)	18.4 (8-42)	95.8 (0-100)	4.2 (0-100)	0
• Weighted mean[2]	20.5	98.9	1.1	0
Liver casserole (n=7/7)				
• Mean (min-max)	14.1 (10-21)	64.5 (0-100)	18.3 (0-100)	17.2 (0-45)
• Weighted mean[2]	13.6	67.5	3.4	29.1

[1]Amount of raw liver component as a percentage of weight of the end product.
[2]Relative to market share.

4.3.2 Size of production run

The size of the production run can affect the run-to-run stability of the final retinoid content of the product. If a large amount of food is produced at a time, the amount of liver used is also large, and livers with high and low retinoid content compensate for each other. On the contrary, if the production run is small with only one or a few livers in a run, the final retinoid content varies more due to chance.

Among Finnish food manufacturers, the sizes of single production runs vary depending on the production volume and the amount of purchase orders. One batch of liver sausage or pâté can use 20-120 kg of liver. For liver casserole, one batch uses around 170 kg of liver among the large manufacturers. Liver patties and liver stew are served in canteens and restaurants in different volumes. Liver foods are also made in small quantities at home. The volumes of liver used in both of these instances can be expected to be lower than in industrial production but are unknown.

4.4 Vitamin A (retinoids) in liver

4.4.1 Sampling and analytical methods

Sampling of liver samples from bovine, swine and chicken and analytical methodology used to determine liver vitamin A content have been explained in detail by Lavikainen et al. (2007). Briefly liver samples were collected from Finnish slaughterhouses during the spring of 2005. Bovine and swine livers were treated as individual samples, but, among chickens, each sample comprised the livers of ten birds from the same producer. All the chickens were slaughtered at the age of 35 days and pigs at the age of six months. The age of bovines varied from 13 months to 12 years.

Pre-treatment of the samples involved sample homogenisation, protein precipitation and liquid-liquid extraction. Retinol, retinyl esters and ß-carotene (only from bovines) were analysed from liver samples with high-performance liquid chromatography (HPLC) using diode array detection at 325 nm. The analysing procedure was based on the methods of Barua et al. (1998) and van Merris et al. (2002).

4.4.2 Retinoid content of livers

Liver vitamin A content (µg RE/g) in each sample was calculated as a sum of the analysed vitamin A activity of retinol and retinyl esters. The vitamin A activity of ß-carotene was not taken into account, because its impact on total vitamin A activity would have been negligible. Liver vitamin A (retinoids) content, used in simulation of retinoid intakes, are shown in Figure 3.

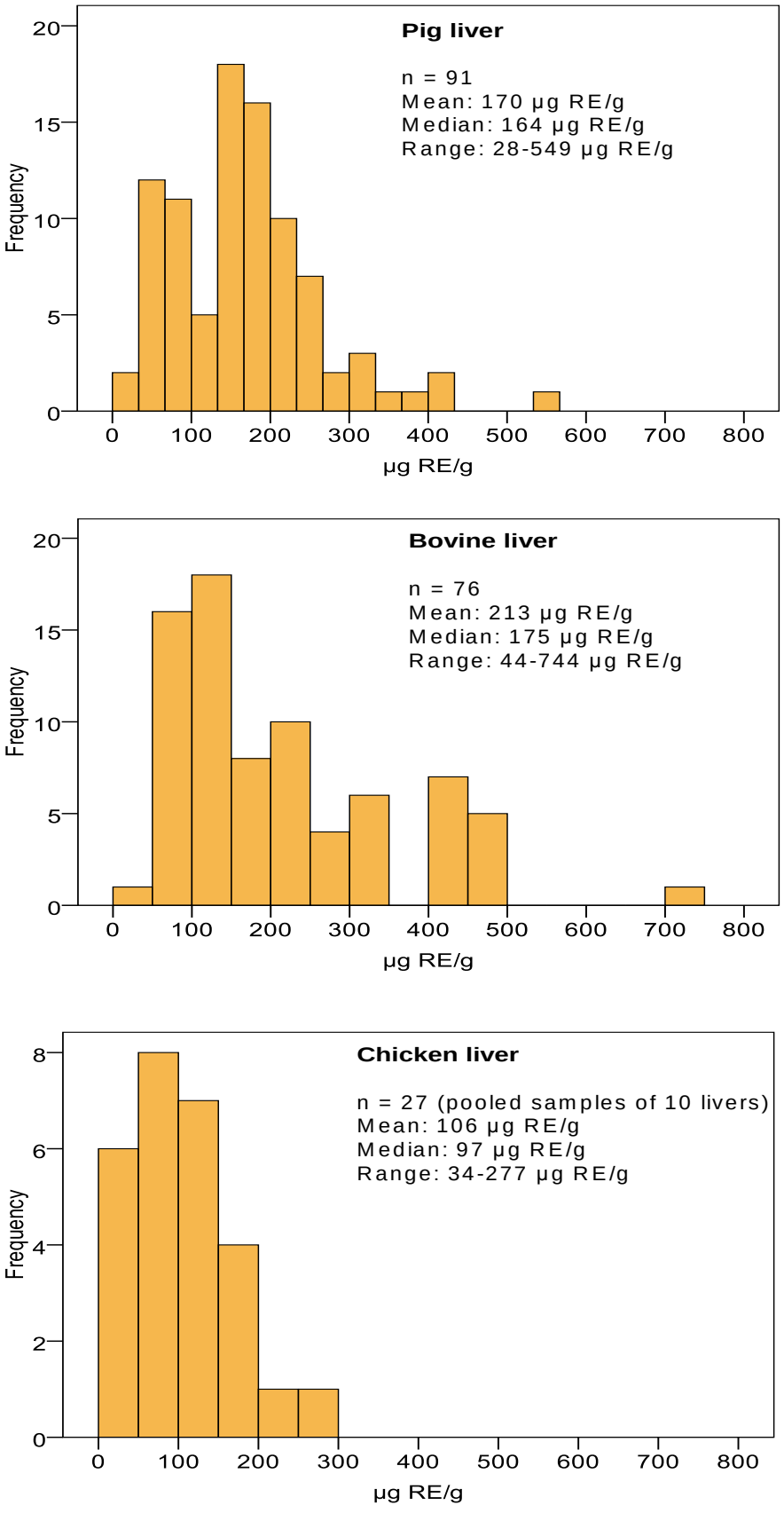

***Figure 3**. Measured liver retinoid content in pigs, bovines and chickens.*

4.5 Daily intake of vitamin A from non-liver sources

Intake estimates of vitamin A from non-liver sources were based on the 3-day DIPP Nutrition Study data. Both natural and supplemental intake was estimated using the method of Nusser and co-workers (1996). The method gives the long-run average of daily intakes (usual daily intake) by taking into account day-to-day correlation and nuisance effects (such as day-of-week and interview sequence). It also allows exceptions from normality through grafted polynomial transformations and recognises the measurement error associated with one-day dietary intakes. Estimates were done using the SAS based SIDE® program. In carotenoid intake calculations, the following ratios were used: 1 µg RE = 12 µg of dietary ß-carotene = 24 µg of other dietary provitamin A carotenoids.

Among 1-, 3- and 6-year-old children, the median intake of total vitamin A from non-liver sources was 235, 329 and 428 µg RE/day respectively and that of retinoids 79, 219 and 290 µg RE/day respectively. Non-liver derived intake was similar among liver eaters and non-liver eaters for both total vitamin A and retinoids. The intake distributions are shown in Figure 4.

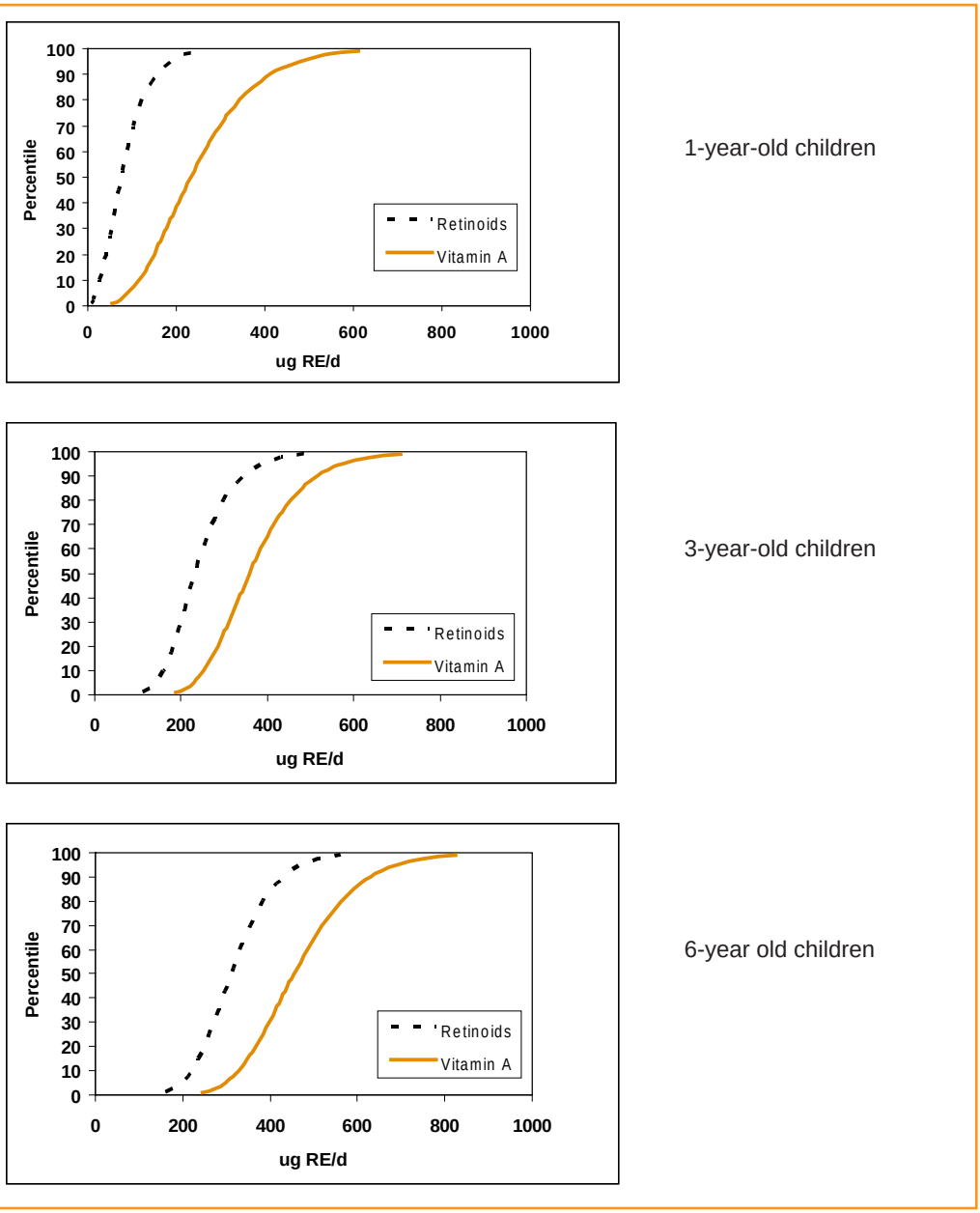

Figure 4. *Reported average daily intakes of non-liver retinoids and vitamin A among 1-, 3- and 6-year-old children in the DIPP Nutrition Study.*

4.6 Simulation models

Simulation models were applied to estimate the combined contribution of non-liver and liver foods on vitamin A and retinoid intake on two different scenarios: long term daily average intake by long term liver consumption and intake from single portions of liver products.

Vitamin A and retinoid intakes were estimated separately for different liver food consumption scenarios (liver sausage or pâté, liver casserole, liver sauce and liver patties) and for different age classes (1-, 3- and 6- year old children).

The simulation models were designed using commercial spreadsheet software (Microsoft Office Excel 2003, Microsoft Corporation, USA), with a commercial add-in module for risk analysis (@Risk, version 4.5.2, Palisade Corporation, USA, 2002). @Risk uses the Monte Carlo method to produce possible outcomes. The results of the simulation model depend on used input values. In the Monte Carlo model, possible input values can be described as probability distributions instead of point estimates. During the simulation process, the chain of events is repeated many times (iterations). New input values are randomly sampled from probability distributions for each iteration. Individual results are then combined to produce a probability distribution for outcome values. Inputs used in the models and empirical parameters on the background of fitted distributions are presented in Appendix 1.

Overall vitamin A and retinoid intake was estimated by summing simulated non-liver and relevant liver contributed vitamin A/ retinoid intakes for each scenario and age-class separately. Distributions of non-liver contributed vitamin A and retinoid intakes were estimated directly from the distributions of DIPP Nutrition Study.

4.6.1 Retinoid content of liver products

Liver content ($cLiver_j$) of each animal species j used in liver products (% in product) and market shares of different products within each product group (M%) were as in the previous Mavira-study (Lavikainen et al. 2007).

The size of livers in swine (1.3-1.8 kg) and bovines (4.8-7.4 kg) were described as uniform distributions while the size of a chicken liver was assumed to be 0.05 kg. Weight of liver mass used in one production batch was assumed to be 100 kg. By simulating average size of livers, it was possible to calculate the approximate number of livers within a certain batch i (n_{ij}) of a certain species j. If the product contained livers of several species this was taken into account by dividing the 100 kg for appropriate sub-proportions before the estimation of n_{ij}.

Measured single liver retinoid content (Mavira-project, Lavikainen et al. 2007) was fitted by @risk to estimate proper distribution assumptions. Most concentrations were approximately log-normally distributed. The parameters were then estimated by bootstrapping to gain three parameters: mean retinoid content of a single liver (mean_cR), standard deviation of single liver retinoid content (std_ cR) and the uncertainty of standard deviation (un_cR) for each species j used for liver products. Uncertainty was assumed to be normally distributed. Retinoid content of a single batch i of a certain liver product (CR_{ij}) contributed by a liver of species j could then be simulated as

$$cR_{ij} = e^{N[\text{mean} = \text{mean\_cR} ; \text{standard deviation} = (N(\text{std\_ cR}); (\text{un\_cR}))/ \text{SQRT}(\text{nij}))]}$$

Where N denotes normal distribution and e ~ 2.7182. The function actually uses the property of normal distribution where the uncertainty of mean could be defined by scaling standard deviation by the square root of the sample size which equals in this context the number of livers of certain species which has been used for a certain product batch i. Because bootstrapping by Auvtools takes into account log-normal assumptions by correcting the parameter estimates appropriately, there was no need for adjusting mean and therefore concentrations could be simulated directly as given in the equation.

Retinoid content of a product batch $_i$ (cR_i) was then estimated by summing simulated retinoid contents CR_{ij} in proportions as appropriate for the recipe ($cLiver_j$). Products were sampled in proportions of market share (M%) to define the

retinoid content of the actual product consumed ($ConsR_i$) in an iteration and eating scenario. The effect of heating was taken into account by multiplying the $ConsRi_i$ by 0.85 which assumes 15% reduction in retinoid content.

4.6.2 Intake of vitamin A and retinoids among DIPP-Nutrition study children

The retinoid intakes were estimated by multiplying retinoid concentration of the liver products by the portion sizes consumed (W) for each subject. Three day averages of DIPP study portion sizes were used, when the average daily intake of vitamin A and retinoids were estimated. In the case of single meal intake of retinoids, the portion sizes that appeared in the DIPP Nutrition Study were used as such. For each simulation, the number of iterations was 30 000.

4.6.3 Proportion and eating frequency of apparent eaters

Only one 3-day food record for each respondent in the DIPP Nutrition Study caused bias for estimation of food consumption frequency of those products which may be used more seldom than once per 3 days. Thus, the lowest observed frequency of any consumption according to the data was once per 3 days. If the population on average is consuming some items more seldom, part of the consumers become apparent non-eaters and show zero consumption during the days of the diary. Eating frequency of apparent eaters becomes overestimated similarly since the lowest frequency is that once per three days. Simultaneously, also the estimation of the proportion of true eaters using those rarely consumed items become biased (Figure 5). These biases are relevant if the safe portion estimate of certain liver products for long term consumption is aimed to be scaled for the relevant frequency of consumption – in other words for the level which is nowadays appearing among the Finnish population of children.

Relevant eating frequency for a population was estimated by zero-inflated poisson regression (Zicounts package, R 2.6.2. software). Both eating frequency among true eaters and the proportion of true non-eaters were estimated simultaneously by zero-inflated poisson regression. Estimates were conditional, which means that if the proportion of non-eaters is over-estimated the frequency of eating among true eaters becomes underestimated. The fitted model had only two intercepts, one for the proportion of true non-eaters and one for the lambda of Poisson distribution, which refers to the eating frequency.

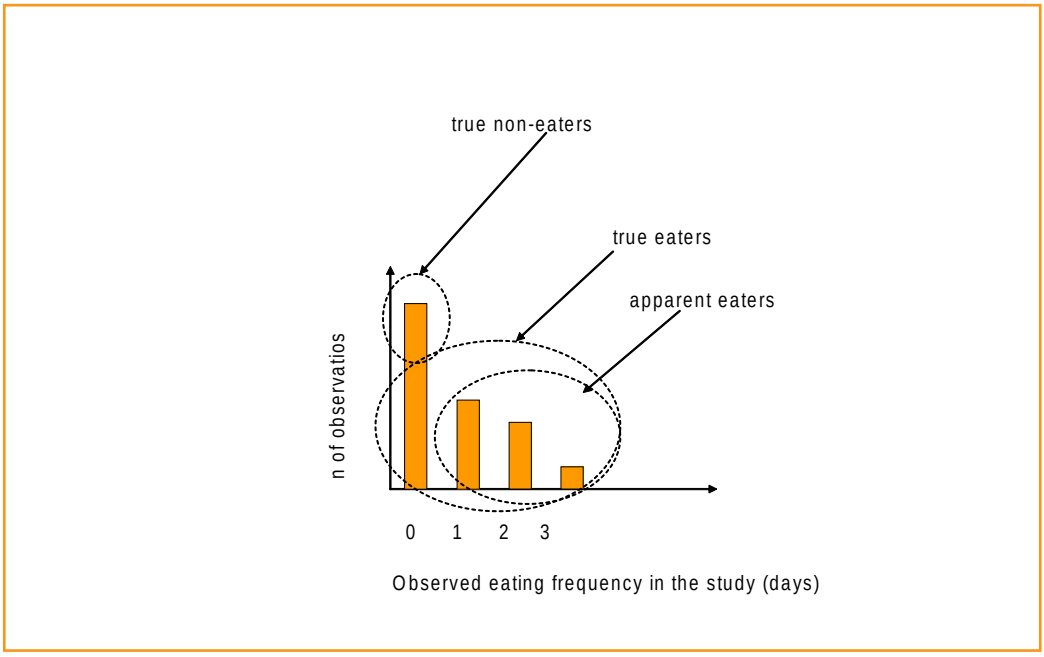

Figure 5. *Schematic illustration of the relationship between true and apparent eaters in short term studies.*

4.6.4 Effect of eating frequency on vitamin A and retinoid intake by long term liver consumption

For studying safe eating frequencies of liver foods, the combined effects of eating frequency and portion size were taken into account. In this simulation, portion W should be thought of in the context of long term average portion size when a certain product is consumed. The applied range of portions was similar as in single portion simulations. They were selected according to the ranges that appeared in the DIPP Nutrition Study for a certain product group and age class: applied distributions were uniform distributions (max=maximum in DIPP Nutrition Study, min=minimum in DIPP Nutrition Study; Table 12). Simulations consisted of 35 000 iterations per eating frequency.

Eating frequency describes here frequency of consumption of a certain liver product. Studied eating frequencies were daily, every second day, every third day, once a week, once every two weeks, once a month and once every two months.

Long term average intake could be estimated by multiplying W by r_{liver} and then multiplying by the sampled value of the appropriate retinoid concentration distribution of the consumed liver product (heat corrected $ConsR_i$). This concentration distribution is the same as used for single portion simulations and may present more variance than production batches of certain products would present in long term follow up studies. By using these values we also simulated a situation when a person is using only one product of a product group. Moreover non-liver contributions were described as three day average non-liver retinoid contributions – so non-liver contribution presents slightly less variation than in single doses. Total long term average retinoid intake was then estimated by summing non-retinoid and retinoid doses of relevant scenarios and age classes.

Table 12. The ranges of liver food portion sizes used in the risk assessment. Ranges were taken from the DIPP Nutrition Study

Age/Liver food	Portion size range (g)
1 year	
Liver sausage and pâté	5-30
Liver casserole	5-180
3 years	
Liver sausage and pâté	2-70
Liver casserole	5-300
Liver sauce	50-150
Liver patties	30-50
6 years	
Liver sausage and pâté	5-80
Liver casserole	5-450
Liver sauce	50-150
Liver patties	30-50

5. Risk characterization

5.1 Retinoids in liver foods

Estimated retinoid content of Finnish liver foods is presented in Figure 6. The mean retinoid content was the highest in liver patties followed in descending order by liver sauce, liver sausage or pâté and liver casserole. The retinoid content varied within the liver food groups reflecting variation both in retinoid content of livers used as an ingredient and in recipes (liver content) of liver foods.

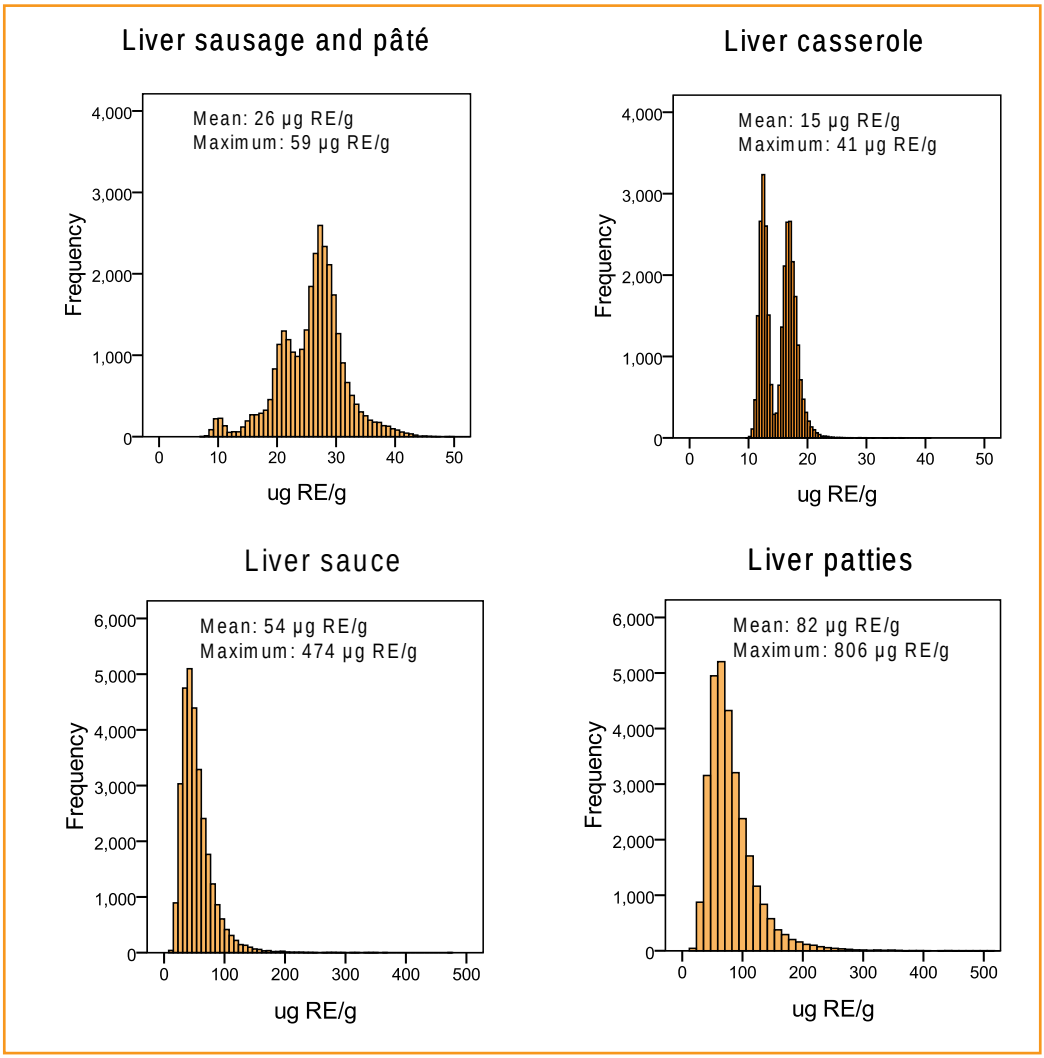

Figure 6. *Retinoid content in Finnish liver foods weighted by market share.*

5.2 Daily intake of vitamin A and retinoids from different sources

Estimated total vitamin A and retinoid intake distributions are shown in Figure 7 and Table 13. The median intake of retinoids was 3.7, 2.7 and 2.5 times higher among 1-, 3- and 6-year-old liver eaters respectively than among non-liver eaters. Independent of the age-group, the median intake of total vitamin A was about 2 times higher among livers eaters than among non-liver eaters (Table 13).

Based on simulation results, retinoids constituted 68%, 82%, and 84% of total vitamin A intake among 1-, 3- and 6-year-old liver eaters respectively, and 40, 67 and 69% of total vitamin A intake among 1-, 3- and 6-year-old non-liver eaters respectively. The importance of liver as a vitamin A source was clear because among 1-, 3- and 6-year-old liver eaters, an average of 56, 57 and 54% of retinoid intake and 39%, 48% and 47% of total vitamin A intake came from liver foods, respectively.

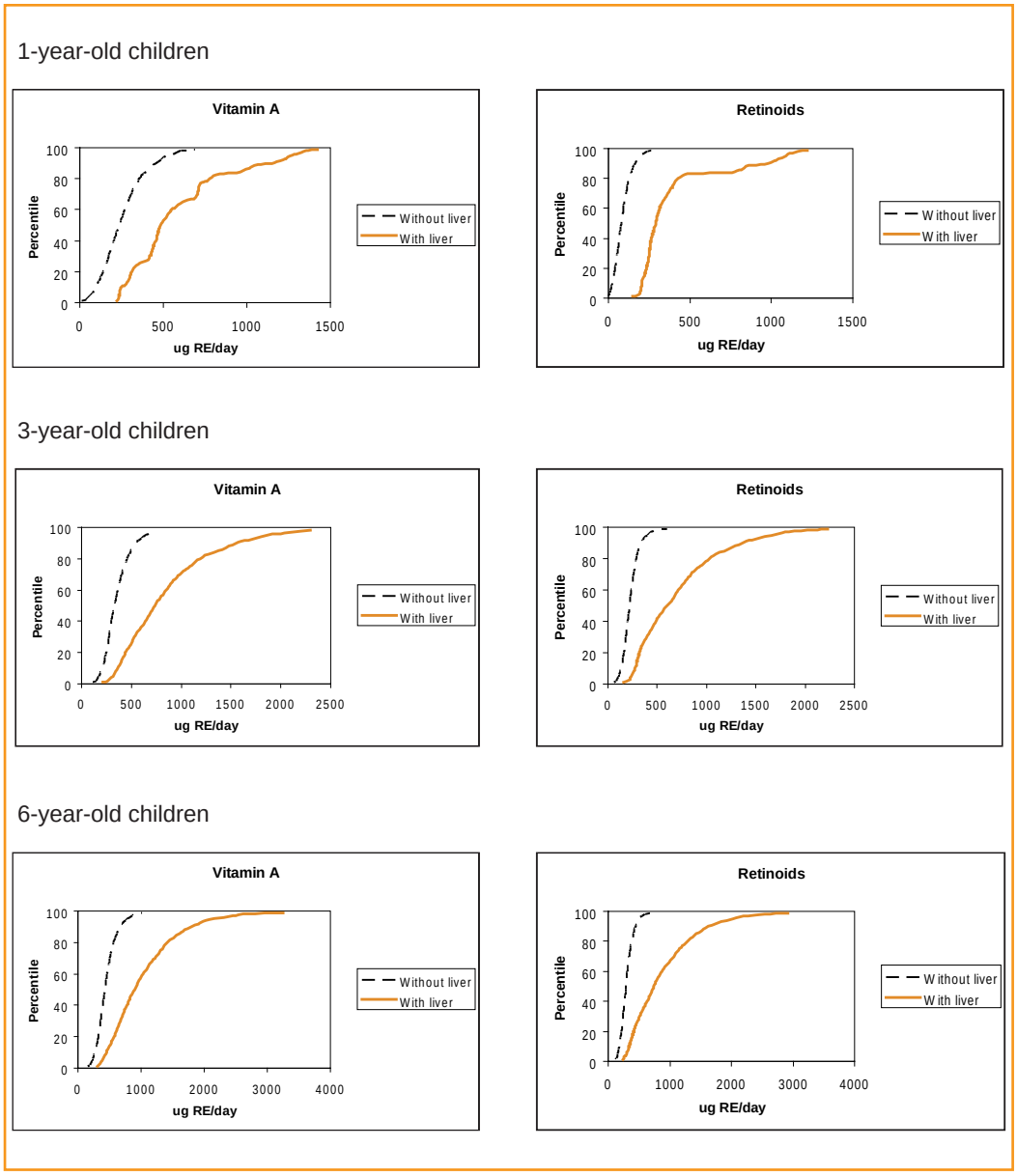

Figure 7. *Daily intakes of vitamin A and retinoids among 1-, 3- and 6-year-old children according to reported food consumption in the DIPP Nutrition Study.*

Table 13. Daily intakes of retinoids and vitamin A among 1-, 3- and 6-year-old children according to reported food consumption in the DIPP Nutrition Study.

Age/Vitamin A and retinoid source	Retinoids (µg RE/day)			Vitamin A (µg RE/day)		
	Median	5th-5th range	Maximum	Median	5th-5th range	Maximum
1 year						
Food with liver[1]	290	197-1087	1416	483	237-1273	1621
Food without liver[2]	79	13-195	559	235	68-527	1028
3 years						
Food with liver[1]	600	238-1656	9900	731	315-1873	10265
Food without liver[2]	219	112-403	1683	329	179-653	1879
6 years						
Food with liver[1]	743	298-2027	9631	895	376-2167	10242
Food without liver[2]	290	154-500	1514	428	232-791	1922

[1]Among liver eaters
[2]Among all children

In table 14, the intake estimates are compared with reference intakes of vitamin A. Sixteen percent (16%) of 1-year-old liver eaters and below 10% of 3- and 6-year-old liver eaters fell below the recommended vitamin A intake, but the average requirement was achieved by everyone. Over half of 1- and 3-year-old and slightly below half of 6-year-old non-liver eaters remained below the recommended intake. Even 41% of 1-year-old and about 10% of 3- and 6-year-old non-liver eaters had an intake below the estimated average requirement.

In table 15, the retinoid intake estimates are compared with upper tolerable intake levels for children. Fifteen percent (15%), 34% and 28% of 1-, 3- and 6-year-old liver eaters respectively, exceeded the recommended upper intake limit. Among non-liver eaters, there was no risk of exceeding the maximum intake limit

Table 14. Daily intakes of total vitamin A in proportion to reference levels among 1-, 3- and 6-year-old children according to reported food consumption in the DIPP Nutrition Study.

Age/Vitamin A source	% of children below reference level	
	< EAR[1]	< RDI[2]
1 year		
Food with liver[3]	0	16
Food without liver[4]	41	68
3 years		
Food with liver[3]	0	8
Food without liver[4]	9	56
6 years		
Food with liver[3]	0	6
Food without liver[4]	11	41

[1]EAR = Estimated average requirement,
1- and 3-year-olds 210 µg RE/day, 6-year-olds 275 µg RE/day
[2]RDI = Recommended daily intake,
1-year-olds 300 µg RE/day, 3-year-olds 350 µg RE/day, 6-year-old 400 µg RE/day
[3]Among liver eaters
[4]Among all children

Table 15. Daily intakes of retinoids in proportion to upper tolerable intake levels among 1-, 3- and 6-year-old children according to reported food consumption in the DIPP Nutrition Study.

	UL[1]	
Age/Retinoid source	**% of children above UL[1]**	**95th percentile / UL[1]**
1 year		
Food with liver[2]	15	1.4
Food without liver[2]	0	0.24
3 years		
Food with liver[2]	34	2.1
Food without liver[2]	0.2	0.50
6 years		
Food with liver[2]	28	1.8
Food without liver[3]	0.1	0.45

[1]UL = Upper tolerable intake level according to SCF 2002:
1- and 3-year-olds 800 µg RE/day, 6-year olds 1100 µg RE/day

[2]Among liver eaters
[3]Among all children

5.3 Eating frequency among true eaters

About 18% of 3- and 6-year-old children reported liver consumption during the DIPP-nutrition study. It is, however, very likely that the real proportion of liver eaters among the study population was higher and part of the responders just didn't happen to eat liver foods during those 3 days when they filled in the food record. The weakness of the consumption data was that it didn't include information about the proportion of liver eaters and non-liver eaters in the real population, i.e., the size of the sub-populations with possible liver consumption over a long period or no liver consumption at all. For these reasons, both eating frequency among true eaters and the proportion of true non-eaters were estimated by zero-inflated poisson regression.

As a result 24% and 21% of 3- and 6-year-old DIPP Nutrition Study children were estimated to be true liver sausage or pâté eaters respectively, and 38% and 44% true liver casserole eaters respectively. True eating frequencies were estimated to be every fourth or fifth day and every second week for liver sausage or pâté and liver casserole respectively (Table 16). For other liver foods (liver sauce and liver patties) and for 1-year-old liver eaters frequencies and proportion estimates were not estimable due to the small amount of information.

Table 16. Approximated point estimates for eating frequencies among 3- and 6-year-old liver eaters by zero-inflated Poisson regression.

Age/Liver food	Eating frequency (1/d)	Proportion of population (%)
3 years		
Liver sausage and pâté	0.20	24
Liver casserole	0.08	38
6 years		
Liver sausage and pâté	0.24	21
Liver casserole	0.07	44

5.4 Single meal retinoid intake

A single meal was defined as an amount of certain liver food eaten in one day. Intake estimates were calculated separately for every liver food studied. The simulated medians, 5th – 95th percentile ranges and maximum intakes are shown in Table 17.

According to Olson (2001), acute toxicity in children may even begin with doses of > 20 x the RDA for vitamin A. This would mean doses over 6 000-8 000 µg RE which are higher than the 95th percentile with any liver food or age group studied except that with 3- and 6-year old liver sauce eaters. Based on meta-analysis, Myhre et al. (2003) however, concluded that the safe upper single dose of retinol in oil or liver for infants and small children is much higher, ~ 3 000 – 3 500 µg RE/kg body weight, whereas water-miscible and emulsified forms of retinol have a lower threshold. This means that harmful single doses of liver for 1-6–year-old children would be over 30 000 – 35 000 µg RE. According to Allen & Haskell (2002), a 30 000 - 60 000 µg dose of retinoids is the level, that may cause acute toxicity for a child over 12 months.

Results in Table 17 show that only less than 1% of liver eaters exceeded the dose 30 000 µg RE. This indicates that there is very low risk to be exposed to harmful doses of retinoids by eating single portions of liver foods.

Table 17. Retinoid intakes (µg RE) from single portions of different liver foods among 1-, 3- and 6-year-old children in the DIPP Nutrition Study. Intakes are calculated from liver only

	Intake from single portion (µg RE)			
Age/Liver food	**Median**	**5th-95th range**	**Maximum**	**% > 30000 µg RE**
1 year				
Liver sausage and pâté	415	119-860	1450	0
Liver casserole	729	64-3062	7135	0
3 years				
Liver sausage and pâté	391	103-1520	3129	0
Liver casserole	1723	253-3532	7927	0
Liver sauce	4822	2520-10203	53329	< 1
Liver patties	2849	1302-6736	35528	< 1
6 years				
Liver sausage and pâté	411	117-1485	4197	0
Liver casserole	2288	450-4658	11891	0
Liver sauce	4471	1822-10904	46529	< 1
Liver patties	2192	1146-4688	21317	0

5.5 Safe long term consumption of liver foods

As seen below, single portions of liver foods used as portion sizes that appeared in the DIPP Nutrition Study, do not very probably expose children to harmful doses of retinoids. Instead there is a risk to exceed upper tolerable intake levels through the long term consumption of liver foods. When considering safe long term consumption of liver foods, in addition to portion size, eating frequency is an important factor.

5.5.1 Safe eating frequency if one liver food is used

The effect of eating frequency on long term retinoid intake was first studied in a situation where only one liver food is used. The studied eating frequencies were daily, every second day, every third day, once a week, once every two weeks, once a month, and once every two months. In the simulation, portion sizes varied in the range that appeared in the DIPP Nutrition

Study and retinoid exposure from liver was added to retinoid exposure from non-liver sources.

The effect of eating frequency on the probability that the tolerable level of retinoid intake is exceeded by eating certain liver food is shown in Appendix 2. Probability here means the probable percentage where the upper limit of retinoid intake in the simulation was exceeded. For long term daily retinoid intake, the upper limits set by SCF (2002) were used. They were 800 µg RE/day for 1- and 3-year-olds and 1 100 µg RE/day for 6-year-olds. The highest risk to exceed the upper limit of retinoid intake is related to the use of liver sauce or patties followed in descending order by liver casserole and liver sausage or pâté. However, all liver foods can be eaten in the portion sizes used in the DIPP Nutrition Study by choosing the proper eating frequency.

Table 18 shows safe eating frequencies for each age group and liver food when the probability that the upper limit of retinoid intake would be exceeded is below 1%. The safe eating frequency means the time period where the shown portion size of liver food can be eaten as one or several portions as the total amount of liver food is at the maximum the shown portion size. As an example, 3-year-olds can eat liver sausage or pâté at a maximum of one 70 g, two 35 g or seven 10 g portions during one week.

When only one liver food is used, safe eating frequency varies from every second day to once every two months depending on the age group, liver food and portion size range. The results show that 1-year-olds could eat the shown portion sizes of either liver sausage or pâté (every second day) and liver casserole (once a week) more often than 3-and 6-year-olds (once a week and once every two weeks respectively). This is due to the smaller portion sizes of liver foods and also lower retinoid intakes from non-liver sources among 1-year-olds.

Consumption of liver sauce and patties was low in the DIPP Nutrition Study. No 1-year-olds had eaten liver sauce or liver patties during a 3-day period. Therefore the consideration of eating frequencies among 1-year-olds was restricted to the consumption of liver sausage or pâté and liver casserole only. Few 3- and 6-year-olds reported the consumption of liver sauce or liver patties. The results of simulations shows that liver sauce (once every two months and once a month among 3- and 6-year-olds, respectively) and liver patties (once a month and once every two weeks among 3- and 6-year-olds respectively) can be eaten more seldom than liver sausage or pâté and liver casserole.

5.5.2 Safe eating frequencies if two liver foods are used

It is usual that liver casserole, sauce and patties are eaten as a main course and liver sausage or pâté as accompaniment. Therefore, the effect of eating frequency on long term retinoid intake was also studied in a situation where two liver foods are used. The studied pairs were 1) liver sausage or pâté and liver casserole, 2) liver sausage or pâté and liver sauce, and 3) liver sausage or pâté and liver patties.

The effect of eating frequency on the probability that a tolerable level of retinoid intake is exceeded when eating two certain liver foods is shown in Appendices 3-5. Table 19 shows the safe eating frequency combinations for the use of two liver products when the probability that the upper limit of retinoid intake is exceeded is below 1%.

Eating liver sausage or pâté once a week seems to be safe in relation to retinoid intake in all studied age groups if main liver courses are eaten more seldom than they can be eaten as only liver food. However, an exception is the pair liver sausage or pâté and liver sauce with 3-year-olds. To eliminate the risk of excessive retinoid intake, 3-year-olds can eat liver sausage or pâté only once every two week and liver sauce at the maximum once every two months. Another exception is the pair liver sausage or pâté and liver casserole among 1-year-olds. Because of smaller portion sizes and lower retinoid intakes from other sources as also seen above, 1-year-olds can eat liver sausage or pâté safely every second day too if liver casserole is consumed at the maximum once every two weeks. In all age groups, the use of main liver courses can be allowed more often if the eating frequency of liver sausage or pâté is decreased.

Table 18. Safe eating frequencies when one liver product is consumed. Upper limits of liver food portion sizes are at most the maximum portion sizes appearing in the DIPP Nutrition Study and the probability, that the upper limit of retinoid intake[1] is exceeded, is <1%.

Age/Product	Upper limit of liver food portion size (g)	Safe eating frequency
1 year		
Liver sausage and pâté	30	Every second day
Liver casserole	180	Once a week
3 years		
Liver sausage and pâté	70	Once a week
Liver casserole	300	Once every two weeks
Liver sauce	150	Once every two months
Liver patties	50	Once a month
6 years		
Liver sausage and pâté	80	Once a week
Liver casserole	450	Once every two weeks
Liver sauce	150	Once a month
Liver patties	50	Once every two weeks

[1]One- and 3-year-olds 800 µg RE/day, 6-year olds 1100 µg RE/day (SCF 2002)

Table 19. Safe eating frequency combinations when two different liver products are consumed. Upper limits of liver food portion sizes are at most the maximum portion sizes appearing in the DIPP Nutrition Study and the probability, that the upper limit of retinoid intake[1] is exceeded, is <1%.

Age/Product	Upper limit of liver food portion size (g)	Safe eating frequency combination, option 1	Safe eating frequency combination, option 2
1 year			
Pair			
Liver sausage and pâté	30	Every second day	Once a week
Liver casserole	180	Once every two weeks	Once a week
3 years			
Pair			
Liver sausage and pâté	70	Once a week	Once a month
Liver casserole	300	Once a month	Once every two weeks
Pair			
Liver sausage and pâté	70	Once every two weeks	
Liver sauce	150	Once every two months	
Pair			
Liver sausage and pâté	70	Once a week	Once every two weeks
Liver patties	50	Once every two months	Once a month
6 years			
Pair			
Liver sausage and pâté	80	Once a week	Once every two weeks
Liver casserole	450	Once a month	Once every two weeks
Pair			
Liver sausage and pâté	80	Once a week	Once every two weeks
Liver sauce	150	Once every two months	Once a month
Pair			
Liver sausage and pâté	80	Once a week	
Liver patties	50	Once a month	

[1]One- and 3-year-olds 800 µg RE/day, 6-year olds 1100 µg RE/day (SCF 2002)

6. Discussion

Risk assessment

When considering the results of this risk assessment, it has to be noted that they have been produced by simulations with uncertainties and hypotheses. The results should be reviewed in concurrence with the assumptions of the model. For instance, retinoid distribution of liver foods used to estimate long term retinoid exposure by liver consumption relates exactly for a certain batch of a certain product. People may also switch between different products and also products may show variation from batch to batch in retinoid content, which may overestimate the range of possible exposures. Because the upper end of retinoid content is, however, the most important, in this assessment the safety margin is mainly increased by a slight overestimation of retinoid intake. This overestimation is dependent on, for instance, the batch size (amount of liver) applied for a certain product (not much is known on this), the duration of a production batch available for consumption by one consumer, size of the liver used in a batch, the variation in sources of liver and feeds used in the farming of animals used as liver sources.

Intake of vitamin A (retinoids) from liver foods

A percentage of Finnish children appeared to consume liver, but there was differences in apparent popularity and frequency of liver consumption. During the 3-day nutrition study period, 12 (1.2%), 150 (18.0%) and 155 (18.2%) of 1-, 3- and 6-year-old children, respectively, reported liver consumption. In all age groups, the most commonly used liver food was liver sausage or pâté, followed by liver casserole. Only a few of the 1-year-olds had consumed any liver foods during the 3-day food record period. None of the 1-year-olds and only a few of the 3- and 6-year-olds had consumed liver sauce or liver patties.

When considering the total daily vitamin A intake from the nutritional point of view, liver consumption has a positive effect. Without liver foods, 41%, 9% and 11% of 1-, 3- and 6-year-old children, respectively, had vitamin A intake below the estimated average requirement. With liver foods, the average requirement was achieved by everyone indicating that liver consumption has a positive value as one of the sources of vitamin A. It should be noted, however, that by using batch related concentration of liver products, we may actually overestimate the proportion below the average requirements in the DIPP Nutrition Study.

True liver eaters

The weakness of the consumption data was that it didn't include any information about the proportion of liver eaters and non-liver eaters in the real population. Therefore, we did not present any population estimates for Finnish children. The results are actually valid only for the DIPP study population and the estimated retinoid exposure is conditional on the liver consumption frequencies and portion sizes of that study.

One way to improve the accuracy of exposure estimation in a real population, is to extend the study period so that it is appropriate for the estimation of foods consumed rarely and to include avoidance questions in the questionnaire. Although exposure from single portions may be more important when rarely consumed foods

are considered, long term exposure is limited by frequency itself. This of course applies only to those toxic materials that do not accumulate in the body.

Only the 3-day food records for each respondent caused the bias for the estimation of food consumption frequency of liver products which may be used more rarely than once per three days. Therefore, no reliable calculations could be done directly to estimate the general intake of vitamin A (retinoids) from liver among liver eaters, and estimated liver consumption reflects only those three-day periods when at least one liver food is eaten which overestimates long term retinoid intake. If the goal is to study exposure by a certain food group, one needs population estimates from other sources and the correlation with the intake of the studied food source. Portion size and eating frequency needs to be calibrated for the relevant range but are usually not needed to estimate for the studied source. Therefore, most concerns for nutritional risk assessment studies should be concentrated on estimation of general exposure: identification of at risk foods and consumer groups, concentrations of at risk food groups and clustering of consumption patterns.

To gain a more realistic understanding of real consumption of liver foods, eating frequency among true eaters and the proportion of true non-eaters was estimated by zero-inflated poisson regression. The model itself is heavily loaded with assumptions as each product is modelled as an independent process so that the consumption of liver sausage or pâté did not influence the estimates of liver casserole and within each product type liver is consumed independently on different days. As a result, slightly over 20% of 3- and 6-year-old DIPP Nutrition Study children were estimated to be true liver sausage or pâté eaters, and about 40% true liver casserole eaters. These percentages are much higher than could be seen on the basis of 3-day food records. True eating frequencies were estimated to be every fourth or fifth day and every second week for liver sausage or pâté and liver casserole respectively, indicating much lower eating frequencies than could be estimated directly according to 3-day observations.

Safe use of liver foods

The simulated daily retinoid intakes were compared with the upper limits set by the Scientific Committee (SCF 2002). For long term daily intake, a maximum intake of 800 µg RE/d was used for 1- and 3-year-old children and 1100 µg RE/d for 6-year-old children. Fifteen (15%), thirty-four (34%) and twenty-eight (28%) percent of 1-, 3- and 6-year-old liver eaters respectively, exceeded the recommended upper intake limit. Among non-liver eaters, there was no risk of exceeding the maximum intake level. When retinoid intakes from single liver meals were reviewed, liver eating didn't lead to retinoid intake above the specified safe level of 30 000 µg RE. For long term daily intake, results indicate that there may be also other relevant retinoid sources, such as fortified foods and food supplements, which should be restricted in order to avoid the possibility of exceeding the upper intake limit.

Safe eating frequencies were estimated for the portion ranges that appeared in the DIPP Nutrition Study for each liver food and age group. The estimates were done for situations where one or two liver foods were consumed. Because liver casserole, sauce and patties are usually eaten as main course and liver sausage or pâté as accompaniment, liver sausage or pâté was considered with each main course. In general, independent of age group (1-, 3- or 6-year olds), safety thresholds are not likely to be exceeded if liver sausage or pâté is eaten in moderate amounts once a week. At the same time only one of the main liver courses can be eaten at the safe eating frequency varying from once a month to once every two months depending on the liver food.

Recommendations

In order to prevent excessive intake of vitamin A, liver-based foods have not been recommended for children under the age of one year since 1990. For toddlers, it has been advised to restrict the consumption of liver-based foods (ground liver patties, liver steak, liver stew, and liver casserole), liver sausage and liver pâté to a couple of meals per month. This risk assessment shows that the restriction of children's consumption of liver foods is still necessary, but the recommendations can be eased as compared to those given in 1990.

7. Conclusions

This risk assessment showed that long term liver consumption may expose children to retinoid intakes higher than what is considered safe. The amount of vitamin A obtained from liver-based retinoids, seems to remain below the safe intake from a single portion. With long term consumption of liver foods however, there is a risk of exceeding upper tolerable intake levels. However, in long term consumption moderate portions of liver foods are still safe as long as they are not consumed too often. The safe portion size and eating frequency depend on the age group and type of liver food. When considering the total daily vitamin A intake from the nutritional point of view, liver consumption has a positive effect. However, the benefits of eating liver can probably be substituted by a well-balanced diet with plenty of vegetables and a reasonable amount of meat without the risk of an excess intake of retinoids.

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Appendix 1. Inputs of vitamin A models.

Input	Distribution/Value	Data source
Retinoid contents in livers (µg RE/g)		Mavira -project
Swine, finishing pigs	Normal [mean=5.00; std=normal (mean 0.51; std= 0.0491)]	
Bovine	Normal [mean=5.18; std=normal (mean=0.59; std=0.066)]	
Chicken	Normal [mean=4.51; std= normal (mean=0.52; std=0.0861)]	
Liver contents in foods (Amount of raw liver component as a percentage of weight of the end product)		
Liver sausage or pâté	Swine 20.4 %, bovine 0.1 %	Finnish food industry
Liver casserole	Swine 8.5 %, bovine 0.5 %, chicken 4.5 %	Finnish food industry
Liver sauce	Swine 16.7 %, bovine 33.3 %	KTL
Liver patties	Swine 11.1 %, bovine 22.2 %	KTL
Heating loss	15 %	Bergström 1994
Size of production run (kg)		
Liver sausage or pâté	70	Assumptions based on information obtained from food industry and literature
Liver casserole	120	
Liver sauce	10	
Liver patties	10	
Portion sizes (g)		DIPP nutrition study 2004-2006
In the model: -daily and single meal intake of vitamin A and retinoids from liver foods among DIPP-study children	Empirical distributions	

Input	Distribution Value	Data source
In models: -effect of eating frequency on vitamin A and retinoid intake and -proportion and eating frequency of apparent eaters		
1-year-olds - liver sausage or pâté - liver casserole	 Uniform(min=5; max=30) Uniform(min=5; max=180)	
3-year-olds - liver sausage or pâté - liver casserole - liver sauce - liver patties	 Uniform(min=2; max=70) Uniform(min=5; Max=300) Uniform(min=50; max=150) Uniform(min=30; max=50)	
6-year-olds - liver sausage or pâté - liver casserole - liver sauce - liver patties	 Uniform(min=5; max=80) Uniform(min=5; max=450) Uniform(min=50; max=150) Uniform(min=30; max=50)	
Vitamin A and retinoid intake from non-liver sources (µg RE/day)		DIPP nutrition study 2004-2006
In model: -single meal intake among DIPP-study children		
1-year-olds	Empirical distributions	
3-year-olds	Binominal[n=1; p=Beta(alpha=95; beta=2356)] = 1: Lognorm[mean=296.34; std=123.64; Shift(-64.952)] Binominal[n=1; p=Beta(alpha=95; beta=2356)] = 0: Uniform(mean=492.44; std=1706.43)	
6-year-olds	Binomial[n=1; p=Beta(alpha=97; beta=2392)] = 1: Lognorm[mean=402.09; std= 150.73; Shift(-96.996)] Binomial[n=1; p=Beta(alpha=97; beta=2392)] = 0: Uniform(mean=626.18; std=1644.67)	

Appendix 2. Effect of eating frequency on the probability that the upper limit of retinoid intake is exceeded when one liver product is consumed at most with the maximum portion sizes that appeared in the DIPP Nutrition Study and when retinoid exposure from both liver and non-liver sources is taken into account. The grey area represents a combination which does not exceed 1% probability for exceeding the upper limit of retinoid intake. Upper limits of retinoid intake are 800 µg RE/day for 1- and 3-year-olds and 1 100 µg RE/day for 6-year-olds.

Age/Liver food	Upper limit of liver food portion size (g)	Probability (%) that the upper limit of retinoid intake is exceeded when eating with the given frequency						
		Every day	Every second day	Every third day	Once a week	Once every two weeks	Once a month	Once every two months
1 year								
Liver sausage and pâté	30	14.8	0	0	0	0	0	0
Liver casserole	180	75.4	48.2	20.8	0	0	0	0
3 years								
Liver sausage and pâté	70	68.8	36.8	11.6	0.2	0	0	0
Liver casserole	300	88.7	75.5	62.3	14.9	0.5	0	0
Liver sauce	150	100	99.7	97.0	62.1	17.3	1.5	0.1
Liver patties	50	100	98.5	87.6	26.4	2.9	0.2	0
6 years								
Liver sausage and pâté	80	63.5	23.9	3.6	0	0	0	0
Liver casserole	450	88.9	77.2	64.8	18.0	0.4	0	0
Liver sauce	150	100	97.9	89.0	37.6	6.2	0.3	0
Liver patties	50	99.8	91.1	66.3	9.6	0.7	0	0

Appendix 3. Effect of eating frequency on the probability that the upper limit of retinoid intake is exceeded among 1-, 3- and 6-year-olds when both liver sausage or pâté and liver casserole are consumed at most with the maximum portion sizes appearing in the DIPP Nutrition Study and when retinoid exposure from both liver and non-liver sources is taken into account. The grey area represents a combination which does not exceed 1% probability for exceeding the upper limit of retinoid intake. Upper limits of retinoid intake are 800 µg RE/day for 1- and 3-year-olds and 1 100 µg RE/day for 6-year-olds.

A) One-year-olds. Upper limit of liver sausage or pâté portion size is 30 g and that of liver casserole 180 g.

Eating frequency of liver sausage or pâté	Probability (%) that upper limit of retinoid intake is exceeded when eating liver casserole						
	Every day	Every second day	Every third day	Once a week	Once every two weeks	Once a month	Once every two months
Every day	91.9	81.7	71.3	41.1	26.5	20.2	17.5
Every second day	84.3	66.1	47.4	5.7	0.5	0.1	0
Every third day	80.9	60.5	37.2	1.2	0.1	0	0
Once a week	78.7	52.3	27.2	0.1	0	0	0
Once every two weeks	76.9	49.9	24.2	0.1	0	0	0
Once a month	75.6	49.2	23.7	0.1	0	0	0
Once every two months	75.1	49.9	21.9	0	0	0	0

B) Three-year-olds. Upper limit of liver sausage or pâté portion size is 70 g and that of liver casserole 300 g.

Eating frequency of liver sausage or pâté	Probability (%) that upper limit of retinoid intake is exceeded when eating liver casserole						
	Every day	Every second day	Every third day	Once a week	Once every two weeks	Once a month	Once every two months
Every day	98.5	97.0	95.0	86.8	79.2	73.8	71.6
Every second day	96.8	92.8	88.4	71.8	55.3	44.7	42.2
Every third day	95.1	89.1	82.1	58.6	33.9	21.0	15.7
Once a week	91.2	81.4	72.3	32.0	4.8	0.8	0.4
Once every two weeks	90.7	78.2	67.3	23.1	1.6	0.1	0.1
Once a month	89.6	77.2	64.4	18.3	0.8	0.1	0
Once every two months	89.1	76.4	63.2	16.4	0.5	0	0

C) Six-year-olds. Upper limit of liver sausage or pâté portion size is 80 g and that of liver casserole 450 g.

Eating frequency of liver sausage or pâté	Probability (%) that upper limit of retinoid intake is exceeded when eating liver casserole						
	Every day	Every second day	Every third day	Once a week	Once every two weeks	Once a month	Once every two months
Every day	98.3	96.1	94.9	86.9	76.7	70.1	67.0
Every second day	96.8	92.0	86.6	68.5	47.9	35.0	29.2
Every third day	94.5	88.3	81.3	54.6	25.1	10.5	6.3
Once a week	91.0	82.1	72.7	32.9	3.3	0.2	0.1
Once every two weeks	90.8	79.8	68.3	24.5	0.9	0.1	0
Once a month	89.9	77.7	67.3	21.2	0.4	0	0
Once every two months	88.5	77.9	65.1	19.6	0.5	0	0

Appendix 4. Effect of eating frequency on the probability that the upper limit of retinoid intake is exceeded among 3- and 6-year-olds when both liver sausage or pâté and liver sauce are consumed at most with the maximum portion sizes appearing in the DIPP Nutrition Study and when retinoid exposure from both liver and non-liver sources is taken into account. The grey area represents a combination which does not exceed 1% probability for exceeding the upper limit of retinoid intake. Upper limits of retinoid intake are 800 µg RE/day for 1- and 3-year-olds and 1 100 µg RE/day for 6-year-olds.

A) Three-year-olds. Upper limit of liver sausage or pâté portion size is 70 g and that of liver sauce 150 g.

Eating frequency of liver sausage or pâté	Probability (%) that upper limit of retinoid intake is exceeded when eating liver sauce						
	Every day	Every second day	Every third day	Once a Week	Once every two weeks	Once a month	Once every two months
Every day	100	100	99.8	97.4	89.6	79.6	74.4
Every second day	100	100	99.8	93.2	75.0	57.0	46.1
Every third day	100	100	99.6	89.2	63.8	34.3	22.2
Once a week	100	99.9	98.9	76.8	33.5	6.4	1.1
Once every two weeks	100	99.9	98.3	70.2	25.4	2.6	0.4
Once a month	100	99.8	97.6	66.6	20.2	2.5	0.1
Once every two months	100	99.8	97.5	63.7	18.4	2.0	0.2

B) Six-year-olds. Upper limit of liver sausage or pâté portion size is 80 g and that of liver sauce 150 g.

Eating frequency of liver sausage or pâté	Probability (%) that upper limit of retinoid intake is exceeded when eating liver sauce						
	Every day	Every second day	Every third day	Once a Week	Once every two weeks	Once a month	Once every two months
Every day	100	100	99.5	94.3	83.0	72.6	68.2
Every second day	100	99.8	98.7	84.2	60.3	39.6	32.6
Every third day	100	99.7	97.8	74.2	40.4	16.4	8.3
Once a week	100	99.1	94.5	55.9	15.0	1.1	0.3
Once every two weeks	100	98.6	92.2	45.2	9.3	0.4	0
Once a month	100	98.4	89.9	41.0	7.4	0.4	0
Once every two months	100	98.4	89.5	38.4	6.7	0.4	0

Appendix 5. Effect of eating frequency on the probability that the upper limit of retinoid intake is exceeded among 3- and 6-year-olds when both liver sausage or pâté and liver patties are consumed at most with the maximum portion sizes appearing in the DIPP Nutrition Study and when retinoid exposure from both liver and non-liver sources are taken into account. The grey area represents a combination which does not exceed 1% probability for exceeding the upper limit of retinoid intake. Upper limits of retinoid intake are 800 µg RE/day for 1- and 3-year-olds and 1 100 µg RE/day for 6-year-olds.

A) Three-year-olds. Upper limit of liver sausage or pâté portion size is 70 g and that of liver patties 50 g.

Eating frequency of liver sausage or pâté	Probability (%) that upper limit of retinoid intake is exceeded when eating liver patties						
	Every day	Every second day	Every third day	Once a week	Once every two weeks	Once a month	Once every two months
Every day	100	100	99.6	92.4	82.6	75.5	72.6
Every second day	100	99.8	98.6	83.1	63.2	49.2	42.8
Every third day	100	99.7	97.7	73.5	41.9	24.4	18.1
Once a Week	100	99.6	94.8	47.6	11.0	1.5	0.5
Once every two weeks	100	99.2	92.3	35.3	5.7	0.3	0.1
Once a Month	100	98.8	89.4	30.8	4.1	0.3	0
Once every two months	100	98.7	88.1	28.1	3.1	0.2	0

B) Six-year-olds. Upper limit of liver sausage or pâté portion size is 80 g and that of liver patties 50 g.

Eating frequency of liver sausage or pâté	Probability (%) that upper limit of retinoid intake is exceeded when eating liver patties						
	Every day	Every second day	Every third day	Once a week	Once every two weeks	Once a month	Once every two months
Every day	100	99.8	98.3	86.9	76.0	68.5	66.9
Every second day	100	99.2	95.0	68.4	46.1	34.4	28.3
Every third day	100	98.3	90.9	49.7	22.1	9.6	5.9
Once a Week	100	96.1	81.7	21.1	3.0	0.3	0.1
Once every two weeks	99.9	93.9	75.1	15.0	1.2	0.1	0
Once a month	99.9	92.5	71.0	11.2	1.0?	0	0
Once every two months	99.8	92.0	67.4	10.3	1.1	0	0

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