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Derivation of an Exposure-Risk Relationship (ERB) or alternatively an Occupational Exposure Limit (AGW) for Selenium and its Compounds

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Abstract

Derivation of an Exposure-Risk Relationship (ERB) or alternatively an Occupational Exposure Limit (AGW) for Selenium and its Compounds

Introduction:
Selenium is an essential element that is present in soil and enters the food chain through plants. Because of its uneven distribution in different geographical regions, the intake of selenium varies hugely worldwide. Occupational selenium exposure can occur in copper smelting and in the production of pigments, glass, rubber, plastics, pharmaceuticals, and electronic devices. The main occupational pathway of exposure is by inhalation.

Objective:
The aim of this epidemiological and toxicological risk assessment of selenium and its compounds is to derive exposure risk-relationships (ERBs) if assessed to be carcinogenic or alternatively, an occupational exposure limit (AGW) based on the most sensitive endpoint, if assessed to be non-carcinogenic and ERBs cannot be derived. Literature that focused on endpoints related to two main potential effects, diabetes and cancer, was reviewed and evaluated.

Diabetes:
Evidence from 14 human studies, including clinical trials of selenium supplementation, case-control, cohort, and cross sectional studies on the association between selenium exposure and type-2 diabetes is conflicting. Three experimental animal studies that administered selenium in the diet investigated endpoints related to diabetes. While these studies provide some insight into biological effects of selenium that might affect glucose homeostasis, they are not sufficient to demonstrate a clear role of selenium in the development of frank diabetes. Mode of action studies reviewed suggest that a U-shaped association between selenoproteins and type-2 diabetes risk might explain some of the apparently contradictory findings in the epidemiology studies.

Cancer:
Evidence from 65 human epidemiological studies on organic selenium compounds suggests an inverse association between selenium exposure and risk of several cancers, especially in men. These data do not provide evidence for any increase in cancer risk associated with intake of organic selenium compounds. Evidence regarding inorganic selenium compounds is inadequate due to a lack of reliable studies. Eleven studies investigated carcinogenicity via the oral route in healthy experimental animals. National Toxicology Program (NTP) studies indicate that ingestion of high doses of selenium sulfide causes liver tumors in rats and mice, but no adequate inhalation studies exist. The available studies were inadequate to address a potential cancer risk in humans under occupational conditions. Selected studies were reviewed that investigated treatment with selenium compounds within the context of initiation-promotion experiments as well as some studies that studied their chemopreventative effects in animal models of different cancers. Results from these studies are conflicting. Depending on study design, timing of selenium exposure during carcinogenesis, and combination with other chemicals, selenium treatment had either a protective role or increased tumor development. The ultimate mechanism of action of the effect of selenium on cancer development has not been established, but mechanistic studies indicate that both low-molecular weight selenium compounds as well as selenoproteins might be involved. Among other factors, polymorphisms in genes encoding for selenoproteins may contribute to the inconsistencies observed in human studies. In numerous studies, sodium selenite, selenate, selenide, and selenium dioxide have been shown to inhibit the genotoxicity of mutagens. By itself, selenium and its inorganic compounds showed some genotoxic potential at high doses, but it is unclear if this activity is expressed at low levels to which humans may be exposed.

Conclusions:
While many studies have investigated the possible association between selenium exposure and the endpoints of diabetes and cancer, no conclusions can be drawn regarding a causal role of selenium in those diseases. Overall the data on cancer and diabetes are not adequate for the derivation of ERBs or an AGW for selenium.

Kurzfassung

Ableitung einer Exposition-Risiko-Beziehung (ERB) oder alternativ eines Arbeitsplatzgrenzwertes (AGW) für Selen und seine Verbindungen

Einleitung:
Selen ist ein essenzielles Element, das im Boden vorkommt und über Pflanzen in die Nahrungskette gelangt. Da das Vorkommen von Selen je nach Region schwankt, ist seine Aufnahme weltweit sehr unterschiedlich. Selenexpositionen am Arbeitsplatz können bei der Kupferverhüttung und bei der Produktion von Pigmenten, Glas, Gummi, Plastik, Arzneimitteln und elektronischen Geräten auftreten. Der wichtigste Aufnahmeweg von Selen sind hier die Atemwege.

Ziel dieser epidemiologischen und toxikologischen Risikobewertung von Selen und seinen Verbindungen ist die Ableitung einer Exposition-Risiko-Beziehung (ERB) für das Krebsrisiko. Sofern ein Krebsrisiko oder eine ERB nicht ermittelt werden kann, ist das Ziel die Ableitung eines Arbeitsplatzgrenzwertes (AGW), basierend auf dem empfindlichsten Endpunkt.

Diabetes:
Die Evidenz für einen Zusammenhang zwischen Selenexposition und Typ-2-Diabetes, die aus 14 Humanstudien (klinische Studien zur Selensupplementierung, Fall-Kontroll-Studien, Kohorten- und Querschnittsstudien) ermittelt werden konnte, ist widersprüchlich. Drei Studien zu Tierversuchen, in denen Selen über die Nahrung zugeführt wurde, untersuchten Endpunkte im Zusammenhang mit Diabetes. Diese Studien geben Hinweise auf die biologische Wirkung von Selen durch den möglichen Einfluss auf die Glucoseregulierung. Für eine eindeutige Rolle bei der Entwicklung von Prädiabetes reichen sie nicht aus. Studien zum Wirkungsmechanismus zeigen einen U-förmigen Zusammenhang zwischen Selenproteinen und einem Risiko für Typ-2-Diabetes, der die z. T. widersprüchlichen Ergebnisse in epidemiologischen Studien erklären könnte.

Krebs:
Die Evidenz aus 65 Humanstudien zu organischen Selenverbindungen zeigt einen inversen Zusammenhang zwischen Selenexposition und dem Risiko verschiedener Krebsarten, besonders bei Männern. Diese Daten liefern keinen Beweis für eine Erhöhung eines Krebsrisikos mit der Aufnahme von organischen Selenverbindungen. Die Evidenz bei anorganischen Selenverbindungen ist unzureichend, da keine zuverlässigen Studien vorliegen. In elf Studien wurde die Kanzerogenität von Selen bei oraler Aufnahme an gesunden Versuchstieren untersucht. Studien im National Toxicology Program (NTP) zeigen, dass die orale Aufnahme hoher Dosen von Selendisulfid bei Ratten und Mäusen Lebertumore verursachen kann, es liegen aber keine entsprechenden Inhalationsstudien vor. Die vorliegenden Studien waren auch unzureichend dafür, ein mögliches Krebsrisiko am Arbeitsplatz zu untersuchen. Einige Studien zur Behandlung mit Selenverbindungen bei Initiation-Promotion-Versuchen sowie Studien, die chemopräventive Effekte im Tiermodell bei verschiedenen Krebsarten untersuchten, wurden näher betrachtet. Die Ergebnisse dieser Studien sind widersprüchlich. Abhängig vom Studiendesign, von der Expositionszeit mit Selen in der Kanzerogenese und der Kombination mit anderen Chemikalien hatte die Behandlung mit Selen einen protektiven oder einen verstärkenden Effekt auf die Tumorentstehung. Der endgültige Wirkmechanismus von Selen auf die Entstehung von Krebs konnte nicht nachgewiesen werden, entsprechende Studien weisen aber darauf hin, dass Selenverbindungen mit einem niedrigen Molekulargewicht und auch Selenproteine einen Einfluss haben. Zudem könnte – neben anderen Faktoren – der Polymorphismus der die Selenproteine codierenden Gene ein Grund für die widersprüchlichen Aussagen sein. In zahlreichen Studien konnte man zeigen, dass Natriumselenit, -selenat, -selenid und Selendioxid die Gentoxizität von Mutagenen hemmten. Selen und seine anorganischen Verbindungen allein zeigten bei hoher Dosierung ein gentoxisches Potenzial, aber es ist unklar, ob dies auch bei geringen Expositionen, denen der Mensch ausgesetzt ist, auftritt.

Schlussfolgerung:
Zahlreiche Studien haben einen möglichen Zusammenhang zwischen Selenexposition und den Endpunkten Diabetes oder Krebs untersucht. Schlussfolgerungen zu einem Ursachenzusammenhang von Selen für diese Krankheiten können aber nicht gezogen werden. Insgesamt sind die bisherigen Ergebnisse zu Krebs und Diabetes nicht ausreichend, um eine ERB oder einen AGW für Selen abzuleiten.

Résumé

Déduction d'une relation exposition-risque ou d'une valeur limite d'exposition professionnelle pour le sélénium et ses composés

Introduction :
Le sélénium est un élément essentiel présent dans le sol, qui entre dans la chaîne alimentaire via les plantes. Sa concentration – et donc son absorption – varient fortement d'une région du monde à l'autre. Une exposition au sélénium sur le lieu de travail peut se produire lors de la fusion du cuivre et de la production de pigments, de verre, de caoutchouc, de plastique, de médicaments et d'appareils électroniques. Dans ces cas, c'est par les voies respiratoires que s'effectue principalement l'absorption du sélénium.

Le but de la présente estimation des risques épidémiologiques et toxicologiques du sélénium et de ses composés est d'en déduire une relation exposition-risque pour le risque de cancer. S'il s'avère impossible de déterminer le risque de cancer ou une relation exposition-risque, le but sera de déduire une valeur limite d'exposition professionnelle basée sur le point final le plus sensible.

Diabète :
L'évidence d'un lien entre l'exposition au sélénium et le diabète de type 2, telle qu'elle ressort de 14 études humaines (études cliniques portant sur la supplémentation en sélénium, études de cas-contrôle, études de cohorte et études transversales) est contradictoire. Trois études effectuées sur des animaux, dans le cadre desquelles du sélénium a été administré dans l'alimentation, ont examiné les points finaux en relation avec le diabète. Il est ressorti de ces études des indications quant à l'action biologique du sélénium via son influence possible sur la régulation du glucose. Ces indices ne suffisent toutefois pas pour en déduire sans ambigüité que le sélénium joue un rôle dans le développement d'un prédiabète. Des études sur le mécanisme d'action font apparaître une relation en forme de U entre les protéines du sélénium et un risque de diabète de type 2, relation qui pourrait expliquer en partie les résultats contradictoires d'études épidémiologiques.

Cancer :
L'évidence résultant de 65 études humaines portant sur des composés organiques de sélénium fait apparaître une relation inverse entre l'exposition au sélénium et le risque de divers types de cancer, en particulier chez les hommes. Ces données ne fournissent aucune preuve que le risque de cancer augmente proportionnellement à l'absorption de composés organiques de sélénium. Concernant les composés anorganiques de sélénium, l'évidence est insuffisante, car on ne dispose pas d'études fiables.

La cancérogénicité du sélénium absorbé oralement a été examinée dans le cadre de onze études menées sur des animaux sains. Il ressort d'études conduites dans le cadre du National Toxicology Program (NTP) que l'absorption orale de fortes doses de bisulfure de sélénium peut provoquer des tumeurs du foie chez des rats et des souris, mais il n'existe pas d'études d'inhalation correspondantes. Les études ne suffisaient pas non plus pour étudier un risque possible de cancer sur le lieu de travail. Certaines études portant sur un traitement à l'aide de composés de sélénium lors d'essais d'initiation/promotion, ainsi que des études portant sur les effets chimiopréventifs dans le modèle animal pour différents types de cancer, ont été examinées de plus près. Les résultats de ces études sont contradictoires. En fonction de la conception de l'étude, de la durée d'exposition au sélénium dans la cancérogénèse et de la combinaison avec d'autres substances chimiques, le traitement au sélénium avait un effet protecteur ou un effet potentialisateur sur le développement de la tumeur. Le mécanisme d'action définitif du sélénium sur l'apparition d'un cancer n'a pu être avéré, mais des études correspondantes semblent indiquer une influence des composés de sélénium de faible poids moléculaire, ainsi que des protéines de sélénium. De plus, le polymorphisme des gènes codifiant les protéines de sélénium pourraient, parmi d'autres facteurs, être l'une des raisons des résultats contradictoires. Dans de nombreuses études, on a pu mettre en évidence le fait que le sélénite, le sélénate et le séléniде de sodium, ainsi que le bioxyde de sélénium, avaient un effet inhibant sur la génotoxicité d'agents mutagènes. À forte dose, le sélénium et ses composés anorganiques présentaient à eux seuls un potentiel génotoxique, mais il n'est pas certain qu'il se fait sentir également en cas de faibles expositions auxquelles est soumis l'être humain.

Conclusion :
De nombreuses études ont examiné la relation possible entre une exposition au sélénium et les points finaux pour le diabète ou le cancer. Aucune conclusion ne peut toutefois en être tirée quant à une relation de cause à effet entre le sélénium et ces maladies. D'une manière générale, les résultats disponibles jusqu'à présent sur le cancer et le diabète ne sont pas suffisants pour en déduire une relation exposition-risque ni une valeur limite d'exposition professionnelle pour le sélénium.

Resumen

Derivación de una ratio exposición/riesgo o alternativamente un nivel máximo de exposición en el puesto de trabajo para el selenio y sus compuestos

Introducción:
El selenio es un elemento esencial que se encuentra en la composición del suelo y que accede a la cadena alimentaria a través de las plantas. Como la proporción de selenio varía según las regiones, la captación es muy diversa en las distintas regiones del mundo. Las exposiciones al selenio en el puesto de trabajo pueden producirse en el recubrimiento de cobre y en la producción de pigmentos, cristal, caucho, plásticos, medicamentos y aparatos electrónicos. La vía de captación de selenio más importante es a través de las vías respiratorias.

El objetivo de esta evaluación de riesgo epidemiológico y toxicológico del selenio y sus compuestos es derivar una ratio exposición/riesgo para el riesgo de cáncer. En caso de que no se pueda calcular el riesgo de cáncer o dicha ratio, el objetivo será derivar un valor límite en el puesto de trabajo basado en el criterio de valoración más sensible.

Diabetes:
La evidencia de una relación entre la exposición al selenio y la diabetes tipo 2 obtenida a través de 14 estudios humanos (estudios clínicos con suplementación de selenio, estudios de casos y controles, estudios de cohortes y de corte) es contradictoria. Tres estudios sobre ensayos con animales a los que se administró selenio a través de la comida analizaron criterios de valoración en relación con la diabetes. Estos estudios resultaron en indicios de que existe un efecto biológico del selenio a través de una posible influencia sobre la regulación de la glucosa, pero estos no son suficientes para deducir que exista una función determinante de esta sustancia en el desarrollo de la prediabetes. Los estudios sobre el mecanismo de estos efectos muestran una relación en forma de U entre las proteínas de selenio y un riesgo de diabetes tipo 2, lo cual podría explicar los resultados contradictorios obtenidos en los estudios epidemiológicos.

Cáncer:
La evidencia obtenida en 65 estudios humanos sobre compuestos orgánicos de selenio muestra una relación inversa entre la exposición al selenio y el riesgo de diversos tipos de cáncer, especialmente en los hombres. Estos datos no suponen ninguna prueba que apunte a un aumento del riesgo de cáncer con la ingesta de compuestos de selenio orgánicas. La evidencia en el caso de compuestos de selenio anorgánicos es insuficiente, ya que no disponemos de ningún estudio fiable. En once estudios se analizó la carcinogeneidad del selenio en la ingesta oral con animales de laboratorio sanos.

Los estudios del National Toxicology Program (NTP) muestran que la ingesta oral de dosis elevadas de disulfuro de selenio puede provocar tumores de hígado en ratas y ratones, pero no disponemos de los estudios de inhalación correspondientes. Además, los estudios existentes resultan insuficientes para analizar la posibilidad del riesgo de cáncer en el puesto de trabajo. Se analizaron en mayor profundidad algunos estudios para el tratamiento con compuestos de selenio en ensayos de iniciación-promoción así como estudios que observaban los efectos quimiopreventivos en un modelo animal con diferentes tipos de cáncer. Los resultados de estos estudios son contradictorios. En función del diseño del estudio, el tiempo de exposición al selenio en la carcinogénesis y la combinación con otras sustancias químicas, el tratamiento con selenio tuvo un efecto protector contra la aparición de tumores o bien fomentó la aparición de los mismos. No se pudo demostrar el mecanismo de funcionamiento definitivo del selenio sobre la aparición del cáncer, pero los estudios correspondientes apuntan a que los compuestos de selenio con un bajo peso molecular y también las proteínas de selenio tienen una influencia sobre estos procesos. Además, un motivo de estos indicios contradictorios podría ser, junto con otros factores, el polimorfismo de los genes que codifican las proteínas de selenio. En numerosos estudios se ha demostrado que el selenito, el seleniato, el seleniuro de sodio y el dióxido de selenio inhibían la genotoxicidad de mutágenos. El selenio y sus compuestos anorgánicos por sí solos mostraron en una dosis elevada un potencial genotóxico, pero no está claro si este efecto se produce también en las exposiciones más breves a las que está sometido el ser humano.

Conclusión:
Numerosos estudios han analizado la posible relación entre la exposición al selenio y los criterios de valoración de la diabetes o el cáncer. No obstante, no se han podido derivar conclusiones sobre una relación causal del selenio en estas enfermedades. En general, los resultados obtenidos hasta la fecha sobre el cáncer y la diabetes no son suficientes para derivar de ello una relación exposición/riesgo o un valor límite para el puesto de trabajo.

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1 Introduction

This status report by October, 2013 presents the results of our evaluation of the toxicity of selenium and its compounds.

ENVIRON has conducted an epidemiological and toxicological risk assessment of selenium and its compounds in order to derive exposure risk-relationships (ERBs) if assessed to be carcinogenic or alternatively, an occupational exposure limit (AGW) based on the most sensitive endpoint, if assessed to be non-carcinogenic and ERBs cannot be derived.

During the course of the project a vast amount of additional literature addressing the possible role of selenium in the diet and as a dietary supplement was identified which could not be disregarded in the derivation of an exposure-risk relationship (ERB).

Literature that focused on endpoints related to two main potential effects, diabetes and cancer, was reviewed and evaluated. The results of this evaluation are reported here.

2 Background

Selenium is an essential micronutrient for humans and animals that is widely distributed throughout the environment, occurring in air, water, soil, vegetation and food. The principal release of selenium into the environment from anthropogenic sources is from coal combustion. Natural sources of selenium include the weathering of selenium-containing rocks and soils, and volcanic eruptions. Selenium is found in most rocks and soils, and naturally occurs at low concentrations in surface waters and groundwaters. Ambient background concentrations of selenium in the air are very low, generally in the nanogram per cubic meter range [1; 2].

Selenium is present in soil and enters the food chain through plants. However, its uneven distribution over the face of the earth results in regions with very low or very high natural levels of selenium in the environment. Humans obtain most of their dietary selenium from bread, cereal, meat and poultry. In contrast to many other micronutrients, the intake of selenium varies hugely worldwide, ranging from deficient (associated with selenium-deficiency diseases like Keshan disease) to toxic concentrations that cause garlic breath, hair and nail loss, disorders of the nervous system and skin, poor dental health, and paralysis, and is governed by geographical differences in available selenium in soil. Additionally, there has been a substantial fall in selenium intake in the United Kingdom and other European Union countries, largely because of the decrease in imports of selenium rich wheat from North America. Dietary selenium intake ranges from 7 µg per day to 4,990 µg per day, with mean values of 40 µg per day in Europe and 93 µg per day (in women) to 134 µg per day (in men) in the USA. Selenium-containing supplements add to these intakes, especially in the USA where 50% of the population takes dietary supplements. Selenium status, as measured by plasma or serum selenium, varies by country and corresponds to intake [3 to 5].

Occupational selenium exposure can occur in copper smelting and in the production of pigments, glass, rubber, plastics, pharmaceuticals, and electronic devices. Selenium is used to make photocells, solar cells, photographic exposure meters, and rectifiers; it is also used as a vulcanizing agent, a glass decolorizer, a photographic toner, and a stainless steel additive [6] (see also [2]).

The main pathway of human occupational exposure to selenium is by inhalation [4].

Various mechanical processes connected with the mining of seleniferous ores or the grinding of selenium compounds can contribute selenium-containing dusts to the atmosphere. In other industrial activities, the amount of selenium released into the air depends on the temperature to which it is heated and on the area available for sublimation and/or vaporization. It is well established that heating amorphous selenium below its melting point results in its sublimation. At temperatures of 170 to 180 °C, traces of selenium can be detected in the air and, at temperatures of 230 to 240 °C, selenium dioxide is released. Heating of amorphous selenium and selenium dioxide resulted in the release of substantial quantities of selenium into the air [4]. However, little quantitative information is available in the literature on levels of human exposure to selenium in industry and the WHO EHC report [4] provides only rather historical information about exposure levels which may not reflect current exposure situation.

More recently, *Schaller* et al. [7] reported results from an air and biomonitoring study at a selenium refining plant. Personal air sampling resulted in exposure levels between 8 and 946 µg/m^3. Serum selenium levels after exposure were between 11.5 and 181.8 µg/l (median 88.7 µg/l) and significantly different from control persons (51.6 and 102.1 µg/l, median 76.1 µg/l). However, they found no correlation between serum selenium levels and air concentration.

3 Diabetes

3.1 Epidemiological studies on selenium exposure and diabetes type II risk

In 2011, the German MAK commission determined the maximum workplace concentration [8] value based on some findings of observational studies and randomized clinical trials in the USA, indicating that high selenium status or selenium supplementation may be associated with an increased risk of type II diabetes. These findings led to an increased research during the past few years with ongoing publications and scientific discussion showing conflicting results.

In observational studies and randomized clinical trials from selenium-replete populations in the US, some findings indicated that high selenium status or selenium supplementation may be associated with an increased risk of type II diabetes [9 to 11] while other did not find an association or even an inverse relationship [12 to 16]. Details of the studies are provided in Table 1 and Table 2 (see page 35 and 38).

A cross-sectional analysis of the US Health Professionals Follow-up Study (HPFS) among men showed statistically significant lower toenail selenium concentrations among men with prevalent diabetes (with or without cardiovascular disease, CVD) than among healthy control participants. A nested case-control study of diabetic men at baseline with incident CVD during an eleven year follow-up period provided non-significantly reduced Odds Ratios (ORs) compared to healthy controls [12].

A cross-sectional analysis among 8,876 adults selected from the US Third National Health and Nutrition Examination Survey (NHANES 1988 to 1994), a probability sample of the US population, showed that subjects in the highest quintile of serum selenium (≥ 137.66 ng/ml) had a significantly increased prevalence of diabetes compared to those in the lowest quintile (‹ 111.62 ng/ml) - OR 1.57 (95% Confidence Interval (CI) 1.16-2.13), based on 1,400 cases [9]. No trend or increase of risk could be observed below the highest quintile of serum selenium. A spline regression model showed an increase in odds for diabetes at › 130 ng/ml with plateau at › 150 ng/ml. Analysis of NHANES 2003 to 2004 data [10] seemed to confirm the association between serum selenium concentrations and the prevalence of type II diabetes found in the *Bleys* et al. study [9] but on a much smaller sample with a higher average serum selenium concentration of 137 ng/ml. Comparing the highest quartile (≥ 147 ng/ml) with the lowest (‹ 124 ng/ml) an OR of 7.64 (95% CI 3.34-17.46) was calculated. An increase of risk was also observed below the highest quartile.

Stranges et al. [11] conducted a post-hoc analysis of the Nutritional Prevention of Cancer (NPC) trial in the Eastern US. In the intervention group (N = 600), selenium was supplemented during 7 to 12 years with 200 µg/day as high-selenium yeast. This supplementation led to an increase in plasma selenium of around 75 ng/ml (derived from Figure 1 in *Stranges* et al. [11], see also [8]). The study showed an increased risk of type II diabetes in the intervention group compared to placebo, particularly in men (not in women) and in participants in the highest tertile of plasma selenium (› 121.6 ng/ml) (Hazard Ratio (HR) = 2.70, 95% CI 1.30 to 5.61).

He et al. [13] examined the association between toenail selenium levels and incidence of type II diabetes in 3,959 young Americans (CARDIA trace element study). Between 1987 and 2005 they identified 234 incident cases of type II diabetes. The hazard ratio in the 5th quintile of baseline toenail selenium was 0.59 (95% CI 0.36 to 0.97) compared to the lowest. However, the study is only published as conference abstract.

Potential association of selenium supplementation on diabetes II risk was evaluated as secondary outcome in the Selenium and Vitamin E Cancer Prevention Trial (SELECT) in 35,533 North American men aged 50 years. Subjects were either supplemented with selenium alone (200 µg/day as selenomethionine), in a combination with Vitamin E or with Vitamin E alone and followed for on average 5.5 years. Despite an increase in serum selenium in both selenium groups from around 135 ng/ml at start to › 250 ng/ml at the final annual visit (measured in a sample), no association between selenium supplementation and diabetes risk was detected (only a small, non-significant increase of risk in the selenium groups compared to the placebo group; Relative Risk (RR) = 1.07, 95% CI 0.94 to 1.22) [14].

Algotar et al. [15] conducted a post-hoc analysis of the small (N = 146) “Watchful Waiting Trial” [17] among persons with non-metastatic prostate cancer. Subjects were randomized to receive 200 or 800 µg of selenised yeast or matched placebo daily and followed over 5 years. Serum glucose levels were obtained every 6 months. Changes in serum glucose levels during the course of the trial were not statistically significantly different for both selenium treatment groups as compared with placebo.

Park et al. [16] performed a prospective evaluation among participants of two US cohorts (NHS and HPFS — nurses and health professionals) with available toenail selenium data, including 3,630 women and 3,535 men, who were free of prevalent diabetes and heart disease at baseline (1982 to 1983 and 1986 to 1987). Diabetes cases were identified by biennial questionnaires and confirmed by a detailed supplementary questionnaire. During follow-up through 2008, 780 cases of incident type II diabetes were identified. After multivariable adjustment, the risk of diabetes was lower across increasing quintiles of selenium, with pooled relative risks across the two cohorts of 1.0 (reference), 0.91 (95% CI 0.73-1.14), 0.78 (0.62-0.99), 0.72 (0.57-0.91), and 0.76 (0.60-0.97), respectively; p for trend = 0.01) for both, men and women. Results were similar excluding those individuals (4%) who used selenium supplements. The inverse relationship between selenium levels and diabetes risk appeared to be linear.

In Europe, two case-control studies showed significantly lower serum selenium concentrations in patients with diabetes than in control subjects [18; 19]. *Navarro-Alacorn* et al. [18] conducted a case control study among 47 diabetic patients with serum

selenium samples and 73 patients with urine selenium samples in Spain. Controls were either healthy adults or institutionalized elderly people. For serum selenium they found a significant lower selenium status in diabetic patients than in healthy controls (although mean serum selenium of healthy controls was only 75 nm/ml) and a small but not significant reduction for urinary selenium. *Kljai* and *Runje* [19] conducted a hospital base case-control study in Croatia. Type-1 and type-2 diabetes groups (31 and 50 cases, respectively) were compared to 62 controls. Significant lower selenium levels were found for both diabetes groups but the authors did not report any control for potential confounding which makes the study unreliable. Both studies were small.

The SU.VI.MAX (Supplementation en Vitamines et Minéraux Antioxydants) trial in France on middle-aged persons found that combined supplementation with antioxidant vitamins and minerals at nutritional doses including selenium (100 µg/day as high-selenium yeast) had no effect on fasting plasma glucose (FPG) after 7.5 years of follow-up, despite a positive association between FPG and selenium concentrations at baseline in the whole population [20].

In the French EVA (Epidemiology of Vascular Ageing) prospective cohort study among an elderly population the highest category of plasma selenium at baseline (1.19 to 1.97 µmol/l or 94 to 156 ng/ml) was associated with a marginally significant decreased risk of onset of impaired fasting glucose or type 2 diabetes in men (HR = 0.50, 95% CI 0.24 to 1.04) but not in women (HR 1.13, 95% CI 0.55 to 2.32), based on 127 incident cases during the 10-year follow-up [21; 22].

Stranges et al. [23] evaluated the association between selenium intake by food and risk of diabetes type 2 cancer among the participants of the ORDET (Hormones and diet in the etiology of breast cancer) cohort in Northern Italy. Selenium intake was estimated through a food frequency questionnaire at end of the 16 follow-up and by using selenium content information through nutritional databases and where no data available, by measurements of food samples. Increase selenium intake was associated with an increased risk of type-2 diabetes. The odds ratio for diabetes comparing the highest to the lowest quintile of selenium intake was 2.39 (95% CI: 1.32, 4.32).

Rayman et al. [24] evaluated the effect of selenium supplementation on plasma adiponectin concentration, "a recognised independent predictor of type-2 diabetes risk" among participants of the UK PRECISE (PREvention of Cancer by Intervention with SElenium) pilot study (N = 473). Participants received either 100, 200 or 300 µg/day as high-selenium yeast over a six-month study period. Despite differences in plasma adiponectin levels at baseline between quartiles of plasma selenium level and a significant increase in plasma selenium levels over this period in all three selenium groups, no difference in plasma adiponectin was found after 6 months supplementation within the groups.

The explanation for the apparently discrepant results of the effect of selenium status and intake on risk of type-2 diabetes is unclear.

Cross-sectional studies as well as case-control studies cannot determine the direction of an observed association, whether increased or decreased selenium level is a cause or a consequence of diabetes due to behavioral or biological effects [5; 9].

Also comparison of studies is difficult. The size of the studies was quite different as well as the baseline selenium levels (especially between Europe and the US) and the general health status of the participants. The level of consideration potential confounders is quite different and none of the studies reported e.g. control for "family history of diabetes". Finally, also the specific exposure metric used in the studies (serum selenium vs. toenail selenium) might have had an influence on results.

In summary, evidence from human studies on selenium and type II diabetes is conflicting [5;25]. *Stranges* et al. [25] and *Rayman* et al. [5; 24] did suggest either an U-shaped association, or, alternatively, that selenium is not causally associated to an increase of type-2 diabetes risk [24].

3.2 Animal studies related to diabetes endpoints

In light of studies in humans that have suggested an association between selenium intake and development of diabetes (e.g., [11; 23; 26]), a number of authors have attempted to use animal models to investigate possible mechanisms by which excessive selenium could influence glucose homeostasis. In particular, three recent studies in animals address certain endpoints pertinent to diabetes. These are a 16-week study in male pigs [27], a one-generation reproduction study in rats [28], and a 3-month study in young male C57BL/6J mice [29]. These studies are briefly described in Table 3 (see page 42). In addition, several studies were identified that investigated the anti-diabetic effect of selenium in animals with diabetes (streptozotocin-induced or knock-out models). These studies have not been reviewed in detail. The literature was also reviewed to identify the potential mechanism of action of selenium on insulin and glucose metabolism.

All three studies have substantial weaknesses that limit their utility for establishing a safe upper level of intake of inorganic selenium that might be useful for deriving an ERB, however. All three involved an experimental group fed a diet containing a normal (adequate) level of selenium and just a single experimental group fed a diet containing an elevated level of selenium. This prevents any evaluation of the shape of the dose-response curve for excessive selenium intake. The two rodent studies also included a group fed a selenium-deficient diet, but that provides no insight into the dose-response relationship for excess selenium intake. Selenium was provided in the form of selenium-enriched yeast in the pig and rat studies, and as sodium selenite in the mouse study. In the selenium-enriched yeast, the selenium is in an organic form (selenoprotein and/or selenomethionine). The relevance of this form of selenium to occupational exposure to inorganic selenium compounds is unclear.

In the one study that used inorganic selenium, *Labunskyy* et al. [29] fed small groups of young male C57BL/6J mice (N = 6 to 7 per group) a selenium-deficient diet, a diet containing a normal adequate level of selenium (0.1 ppm Se), or an elevated level of selenium (0.4 ppm) as sodium selenite. Compared to the mice

fed the adequate selenium diet, the animals fed the high level showed impaired insulin sensitivity (increased plasma glucose levels after i.p. injection of insulin in overnight fasted mice); hyperinsulinemia (increased steady state plasma insulin in fed, but not fasted mice); but no significant changes in steady state plasma glucose levels. Also, liver and kidney extracts of high-dose mice had significantly increased glutathione peroxidase (GPx1) and methionine-R-sulfoxide reductase 1 (MsrB1) activities compared to controls.

Of these effects, the effect on plasma insulin level is limited by the fact that it was measured in just three animals per group. A more robust effect is that of the influence of injected insulin on plasma glucose in fasted animals – measured in 6 or 7 animals/group. In mice fed normal levels of selenium, the injection of insulin was followed by a drop on blood glucose, reaching a minimum (52% of baseline) at 60 minutes after injection, and returning to baseline by 240 minutes (see Table 4, page 43). With the high selenium diet, only a small drop in blood glucose (to 83% of baseline at 60 minutes) was seen.

In the absence of relevant inhalation studies, we investigated whether we could use these data to estimate a tentative safe level of exposure to inorganic selenium above normal. This might be done by treating the excess dietary level of selenium (0.3 ppm above normal) as a lowest-observed-adverse-effect level (LOAEL), and using standard LOAEL/safety factor or Benchmark Dose/safety factor procedures. However, such extrapolation yields tentative safe levels of exposure that are unrealistically low (corresponding to an occupational air concentration of 1.75 µg/m³ or 0.68 µg/m³, depending upon the extrapolation method used – 17.5 or 6.8 µg/day). By comparison, the 2011 MAK value is 20 µg/m³ and the 2012 American Conference of Industrial Hygienists [30] threshold limit value (TLV) is 200 µg/m³ and the Recommended Dietary Allowance [31] for selenium is 55 µg/day.

3.3 Potential mode of action for selenium's impact on glucose metabolism

The full details of how selenium can influence glucose metabolism are not understood, but several hypotheses have been proposed. Selenium has been shown to mimic some of the effects of insulin in isolated rat adipocytes [32], and a number of studies have shown that selenate can induce phosphorylation of the insulin receptor [33]. This activates the insulin signaling cascade [34] and allows association of the insulin receptor substrate with the regulatory subunit of phosphoinositide 3-kinase (PI3K). PI3K in turn activates 3-phosphoinositide-dependent protein kinase 1, which activates serine/threonine protein kinase 2 (AKT2) [35]. Mice lacking AKT2 develop insulin resistance and a diabetes mellitus-like syndrome [36]. Forkhead transcription factors of the FOXO family are important downstream targets of protein kinase B/AKT [37]. FOXO1 confers insulin sensitivity onto glucose 6-phosphatase expression [38]. *In vitro* and *in vivo* studies have shown that dysregulation of expression, localization, and/or activity of any of those proteins may result in insulin resistance [36; 39 to 42].

In addition, the expression and functions of these insulin signal proteins may be affected by selenium via redox or other changes [43; 44]. A total of 24 or 25 selenoprotein genes [45] have been identified in mammals. Over-expression of selenoproteins such as cytosolic glutathione peroxidase (GPx1) and selenoprotein P (SeP) can dysregulate insulin secretion and impair insulin sensitivity [26; 29; 46; 47]. The peroxisomal proliferator-activated receptor gamma coactivator 1 α (PGC-1) represents a key regulator for biosynthesis of the physiological selenium transporter, selenoprotein P, as well as for hepatic gluconeogenesis. Because PGC-1 has been shown to be up-regulated in the livers of diabetic animals and to promote insulin resistance, it has been hypothesized that dysregulated pathways in carbohydrate metabolism and a disturbance of selenium homeostasis are linked via PGC-1 [26].

Both low levels of expression of GPx1 and other stress-related selenoproteins and high levels of expression have been reported to increase insulin resistance and hyperglycaemia [29]. Hence a U-shaped association between selenoproteins and type-2 diabetes risk might explain some of the apparently contradictory findings in the epidemiology studies.

4 Cancer

4.1 Epidemiological studies on selenium exposure and cancer

An evaluation of available human (epidemiological) studies show the lack of occupational cohorts exposed to inorganic selenium compounds by inhalation. There is one poorly described cohort studied by *Glover* [48] including approximately 300 employees exposed in a rectifier (electronics) process over a 26-year period. 17 deaths occurred during follow-up, 6 of which were due to cancer. The difference to the expected number of 5.1 deaths based on national mortality rates was not statistically significant.

Early ecological studies have revealed negative correlations between selenium intake [based on direct or indirect data on consumption (i.e., soil or plant concentration)] or selenium blood levels (based on direct clinical measurement) and cancer incidence or mortality rates. Geographic studies have compared cancer mortality in areas of high vs. low levels of naturally-occurring selenium and reported an inverse relationship between cancer death rates and the selenium concentrations in foliage plants of several Canadian provinces, US States and cities [49 to 51]. The anatomic sites that would come into contact with dietary selenium, such as pharynx, esophagus, stomach, bladder and intestine, showed a substantially lower rate ratio in the high-selenium cities than in the low selenium cities. Other ecological and prospective studies have correlated an increased incidence of colon, breast and other forms of cancer in humans in geographic areas where selenium is deficient (based on estimated dietary intake through food consumption or drinking water) and a lowered cancer incidence with higher selenium concentrations [52 to 54].

Many epidemiological studies (cohort, nested case-control, case-control, clinical trials) have evaluated the effect of oral intake of mainly organic selenium compounds through nutrition or supplementation on the risk of cancer development (for details see Table 5, page 44).

Dennert et al. [55] conducted a systematic review and meta-analysis of 49 observational epidemiological (cohort or nested case-control) studies, published between 1983 and 2009, including 36 nested case-control studies. Case-control studies were excluded. Additionally, six randomised controlled trials were included in this review. The study populations were derived from 42 different cohorts. Twenty-three cohorts were non-randomly recruited, e.g. included volunteers, and 19 cohorts consisted of a random (or total) sample of the population of interest, which was either a specifically exposed population such as male tin-miners in China or the general population. Five studies investigated nutritional and/or supplemental selenium intake, using food-frequency questionnaires or interviews. Forty-three studies assessed biochemical selenium status, toenail specimens, plasma specimens, serum specimens or both.

A meta-analysis was conducted if five or more studies were available for a specific type of cancer (any cancer, female breast cancer, urinary bladder cancer, lung cancer, prostate cancer, stomach cancer and colon/colorectal cancer) comparing highest vs. lowest selenium exposure level.

For total cancer (based on 13 studies), the authors found an inverse association between higher selenium levels and cancer risk for both, incidence (OR 0.69, 95% CI 0.53-0.91) and mortality (OR 0.55, 95% CI 0.36-0.83) which, however, was mainly seen among men not women. These results were confirmed by results of the post-hoc analyses of the NPCT trial [56].

For female breast cancer (based on seven studies), no association was observed (OR 1.00, 95% CI 0.77-1.29). For bladder cancer, a reduced risk was reported (OR 0.67, 95% CI 0.46-0.97), based on five studies. Further studies not included in meta-analysis of *Dennert* [57; 58] confirm this result. Post-hoc analyses of the NPCT trial, however, did not confirm this inverse relationship [56; 59]. A borderline statistically significant risk reduction was observed for lung cancer (OR 0.76, 95% CI 0.57-1.03). Post-hoc analyses of the NPCT trial show in the same direction [56; 59] as it did the meta-analysis by *Zhuo* et al. [60]. A reduced prostate cancer risk was found (OR 0.78, 95% CI 0.66-0.92) based on 14 studies, which was mainly seen in US studies. This result was confirmed in the analysis of the NPCT trial data (as secondary outcome) but not in the SELECT trial, which failed to find any protective effects. A reduced risk was observed also for stomach cancer, even not statistically significant (OR 0.66, 95% CI 0.43-1.01) and a non-significant reduction for colorectal cancers (OR 0.89, 95% CI 0.65-1.23), based on five studies respectively. The post-hoc analyses of the NPCT trial [56] confirmed the risk reduction for colorectal cancers but not the SELECT trial [14]. Five studies on liver cancer including three clinical trials were conducted in China/Taiwan and found reduced risk with higher selenium levels but *Dennert* et al. [55] report about methodological issues related to the clinical trials. No or inconsistent associations were found for other cancers like gynecological or skin cancers.

In summary, human epidemiological data on organic selenium compounds suggest an inverse association between selenium exposure and risk of several cancers, especially in men. These data do not provide evidence for any increase in cancer risk associated with intake of organic selenium compounds. Evidence regarding inorganic selenium compounds is inadequate due to a lack of reliable studies.

4.2 Animal studies

Thirteen studies were reviewed that investigated the impact of various selenium compounds, administered mostly via diet, on cancer development in healthy animals. In addition, several studies, five of which were reviewed, tested the impact of selenium compounds on different stages of carcinogenesis. Further, a number of studies investigated the potential cancer-preventing properties of different selenium compounds in a variety of animal cancer models, including those of prostate, intestinal, mammary, and esophageal cancer, seven of which were reviewed. Doses and experimental conditions that resulted

in preventative or adverse effects on cancer development were reviewed to identify a potential threshold dose. The literature was also reviewed to identify a potential mechanism of action of selenium on cancer development.

4.2.1 Cancer studies in healthy experimental animals

No animal studies that investigated chronic toxicity via the inhalation route were available. Eleven studies that investigated carcinogenicity via the oral route were identified and most of them have been considered in the evaluation of the carcinogenicity of selenium compounds by various institutions (see Table 6, page 50).

Weaknesses of most of these studies have also been discussed in the respective agency reports and in several reviews, e.g., [61; 62]. The study results are here briefly summarized, for details see Table 7a (page 51).

The only selenium compound that has been unequivocally proven to be carcinogenic in both rats and mice is selenium sulfide (SeS), which at high doses caused hepatocellular carcinomas and/or adenomas [63]. The LOAELs were 10.7 and 71 mg/kg/day selenium for rats and mice, respectively.

Sodium selenate and selenite have been studied in several studies that were either not well documented or flawed in design. In summary, these studies showed:

- When selenium was fed at dietary levels of 4 ppm (approximately 0.5 mg/kg/day) and more to rats, there was a drastic increase in mortality, which was attributed to acute toxic hepatitis [64; 65].
- Selenite caused higher mortality than selenate at 2 to 3 ppm selenium in the diet [66; 67]. In these studies, selenate actually increased longevity.
- In some studies in rats and mice at dose levels of 2 to 3 ppm selenium in the diet the total malignant tumor incidence appeared increased. However, lumping tumors from different sites together is not scientifically sound and in addition the results were not adjusted to the increased lifetime of the treated groups versus controls [66; 67].
- When increased incidences of liver tumors with sodium selenate were detected in rats (4.3 ppm in the diet or 0.34 mg/kg/day), they appeared after 18 months of treatment, when large amounts of animals had already died (*Volgarev* and *Tscherkes* [68], as cited in [2]; *Tscherkes* et al. [69], as cited in *Harr* et al. [64]).
- In one study that was conducted for the National Cancer Institute and led ATSDR [2] to conclude *"Allthough the reduced longevity of animals administered 0.4 mg selenium/kg/day might have prevented the observation of some late-developing cancers, the large number of rats necropsied, the end points examined, and the doses administered provide credible evidence of the lack of carcinogenic potential of sodium selenate or selenite."*, the high mortality from toxic hepatitis and a multitude of different diets makes evaluation of the results for selenium difficult [64; 65]. With a LOAEL of 2 ppm selenium in the diet, this study found hyperplastic *in situ* liver lesions that did not regress when selenium was removed from the diet and the authors noted that their high cellular turn-over suggested autonomy. However, no liver tumors were observed.

Treatment with ethyl selenac increased hepatoma (non-metastasized liver tumors) incidence in one strain of mice significantly at a dose of 1.2 mg/kg/day selenium by gavage for three weeks and subsequently 3 ppm in the diet [70]. In this strain, there was also an increased incidence of lymphoma with the ethyl selenac treatment. Subsequently, both effects have been attributed to the thiocarbamate moiety rather than to selenium [1].

Bis-4-acetaminophenyl selenium hydroxide was investigated in two studies of which little documentation was available (*Seifter* et al. [71]; *Seifter* et al. [72], as cited in [73]). Benign liver tumors in rats were noted at dose levels of less than 0.05% in the diet (approximately 6 mg/kg/day selenium).

A naturally seleniferous corn or wheat diet or selenium added as ammonium potassium selenide caused increased cirrhosis incidence after three months and a high mortality in all treatment groups (≥ 5 ppm Se in the diet) [74]. Liver tumors developed only in animals that survived longer than 18 months and had cirrhotic livers, although the authors noted that the degree of cirrhosis and tumor presence was not correlated.

In summary, with the exception of the NTP studies of selenium sulfide, these studies are inadequate to address a potential cancer risk in humans. Under occupational conditions, the relevance of a high dose oral gavage study [63] is questionable.

Conclusions by institutions

The International Agency for Research on Cancer (IARC) [1] concluded *"Although in one experiment in rats selenium produced an increase in the incidence of liver tumours, the available data are insufficient to allow an evaluation of the carcinogenicity of selenium compounds"*. Selenium was subsequently categorized as Group 3 Not classifiable as to its carcinogenicity to humans by IARC in 1987 [75].

In their Integrated Risk Information System (IRIS) review 1993, the US Environmental Protection Agency (EPA) [76] concluded that the animal carcinogenicity data was *"Inadequate. The carcinogenicity of selenium compounds has been evaluated in several animal studies. However, the data are conflicting and difficult to interpret because of apparent anticarcinogenic activity and high toxicity of some selenium salts. In addition, comparison of the available data is difficult because several different salts with varying degrees of bioavailability were used in the assays."*

The German MAK-Commission [77] concluded in 1999 that in rats, sodium selenate was weakly genotoxic *in vivo* [78] and had weak carcinogenic potential based on a limitedly assessable study [67]. Selenium sulfide was weakly clastogenic *in vivo* [79] and only induced an increased number of hepatocellular carcinoma in rats and mice in the range of the maximum tolerated dose and bronchioalveolar adenoma and carcinoma in female mice [63]. Based on these results both sodium selenite and

selenium sulfide were categorized as category 3B carcinogens. Other selenium compounds were thought to have similar effects and are reductively metabolized similarly to sodium selenate; they were categorized in the same category. In 1999, the German MAK-Commission [8] referred to its previous evaluation due to the lack of new studies.

The NTP-Report on Carcinogens, 12th edition [80] concluded in 2011 *"Selenium sulfide is reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in experimental animals"*.

4.2.2 Initiation-promotion studies and studies in animal models of various cancers

In addition to the cancer studies in healthy animals, selected studies were reviewed that investigated treatment with selenium compounds within the context of initiation-promotion experiments as well as some studies that studied their chemopreventative effects in animal models of different cancers (for details see Table 7b, page 58)

A large number of animal studies has been conducted at selenium doses higher than those received from normal standard diets to investigate its chemopreventive effect (as reviewed in [81]). These studies have included models that used chemical- or virus-induced cancers, transplanted or injected tumors or animal strains with high spontaneous tumor rates. In their review, *Gromadzinska* et al. [81] noted that *"two-third of these experiments provided evidence for high doses of selenium reducing cancer development to a moderate extent (15 to 35% in relation to controls), in the majority of cases the reduction being quite significant."* These authors also noted that the anti-carcinogenic effect of selenium was optimal prior to or in the early stages of tumor development.

On the other hand, in a rat model of esophageal adenocarcinoma, 1.7 ppm sodium selenate in the diet (10x the standard diet selenium content) resulting in an approximate dose of 0.13 mg/kg/day starting before the surgery and up to 40 weeks past, increased the tumor incidence over operated controls from 68 to 90% [82]. The MAK-Commission decided that the unusual design of the study did not make it suitable for the assessment of selenium's carcinogenic potential.

Results from several cancer initiation-promotion studies are conflicting [83 to 85]. These studies showed that under certain circumstances and times during carcinogenesis, selenium treatment had a protective role on tumor development, while within the same studies at other times and/or in combination with different chemicals it actually increased tumor development.

4.3 Potential mode of action for selenium's potential impact on cancer

While the ultimate mechanism of action of the effect of selenium on cancer development has not been established, both low-molecular weight selenium compounds as well as seleno-proteins might be involved. Among other factors, polymorphisms in genes encoding for seleno-proteins may contribute to the inconsistencies observed in human studies. Below, some examples of potential modes of action are described that have been proposed to be involved in modulating cancer responses.

At least 25 human seleno-proteins are known serving different physiological functions (reviewed in [86]). It has been suggested that there is a hierarchy of these proteins, with some of the proteins much more sensitive than others to varying selenium intake [87; 88]. For example, glutathione peroxidase-1 (GPX-1) and 15 kD selenoprotein (SeP15) are thought to be particularly sensitive to selenium intake. Decreased GPX-1 expression has been observed in many cancers (as reviewed in [88]). Studies have suggested that supplemental selenium is protective against some cancers at least in part through GPX-1. Other proteins, as well as other low molecular weight selenium compounds might also been involved in cancer-protective effects of selenium [89].

GPX-1 is thought to modulate intracellular reactive oxygen species and thus prevent oxidative damage (e.g., DNA oxidation) and inflammation (as reviewed in [88]). On the other hand it may also block apoptotic cell death, which might allow survival of transformed cells. In their review, *Lubos* et al. [88] suggested that the overall redox state of a cell might influence whether excess GPX-1 is protective or detrimental to its survival. GPX-1 expression as measured in blood and erythrocytes is considered only reflective of selenium deficiency but not of overexposure [2].

Similarly, recent studies have suggested that SeP15 might have a role in the promotion and sustaining of colon cancer [90]. For example, down-regulation of SeP15 inhibited tumorigenicity and metastasis of colon cancer cells [89].

Further, selenium's essential role in the immune system is generally accepted. However, for example, *Koller* et al. [91] showed an increase in natural killer (NK) cell activity in rats after selenium administration, while other specific immune functions were reduced. These authors suggested that NK-sensitive tumors might be responsive to selenium therapy, while NK-insensitive tumors might be enhanced, because humoral and cell-mediated immunity were impaired.

5 Genotoxicity

In numerous studies, sodium selenite, selenate, selenide, and selenium dioxide have been shown to inhibit the genotoxicity of mutagens [92 to 101].

5.1. *In vitro*

Sodium selenite itself was not mutagenic in the presence and absence of a metabolic activation system, up to a concentration of 0.1 mg/plate, in *S. typhimurium* TA98, TAl00, TA1537 or TA1538 [98; 102 to 106]. However, at higher concentrations (2.4 mg/plate) it was mutagenic without metabolic activation in TA100 [105] and at 4.0 mg/plate in TA104 [107]. Without metabolic activation sodium selenate was also mutagenic in *S. typhimurium* TA1534 and TA1535 and weakly mutagenic in TA100 [102; 104; 105]. No mutagenicity was observed in TA98 or TA1537 [105]. Selenium sulfide was mutagenic in *S. typhimurium* TA97 and TA100 in the presence and absence of metabolic activation system [108]. Data on other *in vitro* genotoxicity endpoints are summarized in Table 8, see page 63.

5.2 *In vivo*

Sodium selenite, sodium selenate and selenious acid did not induce somatic mutations or recombination in the wing spot test in *Drosophila melanogaster*, and all three reduced the genotoxic effect of co-administered potassium dichromate [109].

Administration of sodium selenite (0.004 to 0.05 mg selenium/kg body weight/day, oral or intramuscular) for a period of one to 13.5 months, produced no increase in chromosomal aberrations or sister chromatid exchange (SCE) in lymphocytes of 11 patients with neuronal ceroid lipofuscinosis or five normal subjects [110].

After two oral doses of 16.2 mg selenium/kg as selenium sulfide in the rat (about 60% of the LD50), increased DNA damage was detected in the liver [111].

Sodium selenite increased the number of sister-chromatid exchanges in the bone marrow of Chinese hamsters at 3 mg selenium/kg body weight, but not in NMRI mice at 0.8 mg selenium/kg body weight [110; 112].

In two independent experiments, selenium sulfide administered one or three times at intervals of 24 hours by intraperitoneal administration at 2.7 to 14.2 mg selenium/kg body weight produced no increase in micronuclei in the bone marrow of B6C3F1 mice, though cytotoxicity was seen at 14.2 mg selenium/kg body weight [79; 113]. After intraperitoneal administration of sodium selenite (at doses up to 10.7 mg selenium/kg body weight) no increase was seen in the frequency of micronuclei in the bone marrow of mice evaluated 24 hours after dosing. In a parallel experiment, selenious acid at up to 1.5 mg selenium/kg body weight did not increase the micronucleus frequency, but increased micronuclei and cytotoxicity were reported at 3.0 mg selenium/kg body weight [114].

Intramuscular administration of sodium selenite in female BALB/c mice (two doses at a 24-hour interval), increased the micronucleus frequency (assessed 24 hours after the last treatment) starting at the lowest dose tested (0.2 mg selenium/kg body weight), though in a previous study, the authors did not see an increase in chromosome aberrations and no change the mitotic index with the same doses [115]. Details of the doses administered are unclear, however.

No induction of micronuclei was observed in the bone marrow of long-tailed macaque fetuses whose mothers received 0, 0.15 or 0.3 mg L-selenomethionine/kg (0.01, 0.06 or 0.12 mg selenium/kg body weight) by gavage on gestation days 20 to 50. Maternal and fetal toxicity was reported at 0.06 mg selenium/kg body or more [116].

No increase in chromosome aberration frequency in the bone marrow of mice was found after administration of sodium selenite at up to 2.3 mg selenium/kg body weight [110; 117]. Dose-related increases in chromosome aberrations in the bone marrow of mice were reported after oral administration of sodium selenite or sodium selenate at 3.2 and 5.9 mg selenium/kg. Cytotoxicity was seen at doses as low as 3.2 and 2.9 mg selenium/kg [78; 118]. Intraperitoneal administration of selenium sulfide in mice at 7.1 mg selenium/kg body weight increased the frequency of chromosomal aberrations evaluated 36 hours after dosing [79].

An increased chromosome aberration incidence was detected in the bone marrow of Chinese hamsters after a single intraperitoneal dose of 3 mg selenium/kg body weight as sodium selenite [112].

After a single intravenous administration of sodium selenite at up to 2.74 mg selenium/kg body weight, no significant increase in chromosomal aberrations were seen in the bone marrow of rats 24 hours later, but increases were seen when sodium selenite was administered intravenously twice (48 and 24 hours before examination) at 2.28 and 2.74 mg selenium/kg body weight [119].

No increase was seen in the frequency of chromosome aberrations in bone marrow and spleen in rats 24, 36 or 48 hours after oral dosing with selenium sulfide at 35.5 mg selenium/kg body weight [120]. No increase in frequency of chromosome aberrations in peripheral lymphocytes of rats was found after administration of sodium selenite at 2.8 mg selenium/kg body weight [119].

There was no increase in the number of chromosome aberrations in the spermatocytes of mice measured 24 hours after a single intraperitoneal dose of 0.8 mg selenium/kg body weight (equivalent to 1/5 of the LD50) as sodium selenite [110].

In summary, *in vitro*, selenium and its inorganic compounds showed genotoxic effects. In animal studies, positive results were seen in the micronucleus test and the test for chromosomal

aberrations at doses that are close to the LD50. The clastogenic potential observed *in vitro* occurred in vivo only at extremely high doses. No valid genotoxic effects were observed in *in vivo* studies at doses of 1.5 mg selenium/kg body weight or less [110; 112; 114]. This includes a test for germ cell mutagenic effects – induction of chromosome aberrations in spermatocytes [110].

6 Conclusions

While many studies have investigated the possible association between selenium exposure and the endpoints of diabetes and cancer, no conclusions can be drawn regarding a causal role of selenium in those diseases. Evidence from human studies for a role of selenium in type II diabetes is conflicting. Animal studies, while providing some insight into biological effects of selenium that might affect glucose homeostasis, are not sufficient to demonstrate a clear role of selenium in the development of frank diabetes.

Human epidemiological data on organic selenium compounds suggest an inverse association between selenium exposure and risk of several cancers, especially in men. These data do not provide evidence for any increase in cancer risk associated with intake of organic selenium compounds.

Evidence regarding inorganic selenium compounds is inadequate due to a lack of reliable studies. Data from animal studies indicate that ingestion of high doses of selenium sulfide causes liver tumors in rats and mice, but no adequate inhalation studies exist, and studies of other forms of selenium are inadequate to reach a conclusion regarding cancer risk in humans. While there is some evidence of genotoxic potential of high doses of selenium, it is unclear if this activity is expressed at low levels to which humans may be exposed.

Overall the data on cancer and diabetes are not adequate for the derivation of ERBs or an AGW for selenium.

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Table 1:
Characteristics of human studies on diabetes type 2 and selenium

Reference	Study/Cohort	Study Year	Country	Design	Size	Exposure determination	Outcome definition and determination
Navarro-Alarcorn et al. [18]	Diabetes patients and health adults in south-eastern Spain	Before 1995	Spain	Hospital-based case-control	47 cases serum (6 type 1) – 79 cases urine, 223 controls (130 health adults and 93 institutionalized elderly people)	Serum und urine selenium	Hospital
Kljai and *Runje* [19]	Diabetes patients and health adults in Kroatia	Before 2000	Croatia	Hospital-based case-control	31 cases type 1; 50 case type 2 - controls: 62 health blood donnors	Serum selenium	Hospital
Rajpathak et al. [12]	Male participants of the Health Professionals Follow-up study (HPFS) cohort	1987	US	Cross-sectional; nested case-control	Participants with available toenail samples **Cross-sectional:** prevalent diabetes in 1986 (N = 688), prevalent diabetes and CVD (N = 198); health controls (N = 361) **Case-control:** prevalent diabetes at baseline and incident CVD during follow-up (till 1998) (N = 202) matched controls by age, smoking status, date when toenail clippings were sent (N = 361)	Toenail selenium	Self-report (questionnaire), validated in a subsample; for CC additionally medical records or death certificate
Czernichow et al. [20]	SU.VI.MAX clinical trial on middle aged persons	1994 to 2002	France	Clinical trial	1,285 men and 1,861 women with complete data at end of follow-up Persons with FPG ≥ 7 mmol/L or use of anti-diabetic drugs at baseline excluded	Serum selenium	Measurement of FPG
Bleys et al. [9]	Adult participants of the Third National Health and Nutrition Examination Study (NHANES III)	1988 to 1994	US	Cross-sectional	8,876 participants ≥ 20 years of age with complete data 1,379 cases	Serum selenium	FPG ≥ 126 mg/dL or self-report of diabetes or use of anti-diabetic drugs
Stranges et al. [11]	Participants of the Nutritional Prevention of Cancer (NPC) trial	1983 to 1996	US	Clinical trial	1,202 participants without type II diabetes at baseline Mean age: 63 years Mean follow-up: 7.7 years Selenium group: 58 cases Placebo group: 39 cases	Plasma selenium Supplementation with 200 µg Se/day (as yeast)	Self-report during clinical interview, reported use of anti-diabetic drugs, reports in medical documents plus review of medical reports
He et al. [13]	Participants of the CARDIA Trace Element Study	1987 to 2005	US	Cohort	3, 959 young Americans, aged 20 to 32 years and who were free from type 2 diabetes at baseline N = 234 cases	Toenail selenium at baseline	Follow-up clinical examinations details not available (published only as conference abstract)

Table 1 (continued)

Reference	Study/Cohort	Study Year	Country	Design	Size	Exposure determination	Outcome definition and determination
Laclaustra et al. *[*10]	Adult participants of the National Health and Nutrition Examination Study (NHANES)	2003 to 2004	US	Cross-sectional	917 participants ≥ 40 years of age with complete data 121 cases	Serum selenium	FPG ≥ 126 mg/dL or self-report of use of anti-diabetic drugs
Lippman et al. [14]	Participants of the Selenium and Vitamin E Cancer Prevention Trial (SELECT)	2001 to 2008	US, Canada, Puerto Rico	Clinical trial	35,533 healthy men older than 50 years (median age › 62) 4-group trial: placebo vitamin E + placebo selenium + placebo selenium + vitamin E	Serum selenium Supplementation with 200 µg Se/day (from L-selenomethionine)	Self-report of diabetes or use of anti-diabetic drugs (of glitazone class) during clinical interviews; Determined only since 2005 or 2003, respectively Prevalent cases at start excluded
Akbaraly et al. [22] *Coudray* et al. [21]	French vascular aging cohort – EVA elderly population	1991/93 to 2000/2002	France	Prospective cohort	574 men, 815 women at baseline – 1,162 normoglycemic and not using anti-diabetic drugs (635 end of follow-up) Dysclycemia: 127 Diabetes type II: N = 29	Plasma selenium at baseline	FPG ≥ 7mmol/L or use of anti-diabetic drugs + IFG (FPG ≥ 6.1)
Algotar et al. [15]	Participants of the Watchful Waiting Trial on the effects of selenium supplementation on prostate cancer progression	1991 to 1996	US	Clinical trial	146 participants with confirmed non-metastatic prostate cancer Mean age: 73 years	Serum selenium Supplementation with either 200 or 800 µg Se/day (as yeast)	Serum glucose level, measured each six months (not FPG); Participants who reported having diabetes at baseline (N = 19) and during the trial (N = 6) excluded from analysis

Table 1 (continued)

Reference	Study/Cohort	Study Year	Country	Design	Size	Exposure determination	Outcome definition and determination
Stranges et al. [23]	Participants of the ORDET (Hormones and diet in the etiology of breast cancer) study	1987 to 1992 to 2006/2007	Italy	Cohort	7,182 healthy women, age 34 to 72 who compiled the food frequency questionnaire and were free of diabetes at baseline and did not die on other causes than diabetes during follow-up N = 253 cases	Selenium intake estimated based on food frequency questionnaire through nutritional database and where no data available, by measurements of food samples	Presence of at least three of the following: 1) a self-report of a physician diagnosis in the follow-up questionnaire; 2) a self-report of use of insulin or oral hypoglycemic medication in the follow-up questionnaire; 3) evidence of a prescription for insulin or oral hypoglycemic medication by linkage with regional prescription drug database; or 4) a hospital discharge record with the diagnosis of diabetes by linkage with medical discharge records.
Park et al. [16]	Two U.S. cohorts – nurses and health professionals (NHS and HPFS)	1982 to 1983/ 1986 to 1987 to 2008	US	Prospective cohort	3,630 women 3,535 men Diabetes type II: N = 780	Toenail selenium from nested-case control studies	Self-report (questionnaires) FBG ≥ 7 mmol/L or use of antidiabetic drugs
Rayman et al. [24]	Participants of the UK PRECISE (PREvention of Cancer by Intervention with Selenium) pilot study	2000 to 2002 (six months follow-up)	UK	Clinical trial	473 men and women, age: 60 to 74 years	Plasma selenium Supplementation with either 100, 200 or 300 µg Se/day (as yeast)	Plasma adiponectin

Table 2
Results of human studies on diabetes type 2 and selenium

Reference	Study/Cohort	Design	Results	Confounders considered	Comment
Navarro-Alarcorn et al. [18]	Diabetes patients and health adults in southeastern Spain	Hospital-based case-control	Serum selenium significant lower among diabetic patients; urine samples no significant relationship Serum selenium: Mean value control (healthy adults): 74.9 ng/ml Mean value control (elderly): 76.0 ng/ml Mean value case: 64.9 ng/ml ($p < 0.05$) Urinary selenium: Mean value control (healthy adults): 20.2 ng/ml Mean value case: 18.8 ng/ml	Age Gender Type of diabetes Transaminases Serum lipids	
Kljai and *Runje* [19]	Diabetes patients and health adults in Kroatia	Hospital-based case-control	Serum selenium significant lower among diabetic patients (both groups); no significant difference between diabetes groups Mean value control: 64.2 ng/ml Mean value case (type I): 58.2 ng/ml ($p < 0.05$) Mean value case (type II): 59.2 ng/ml ($p < 0.05$)	No control of any potential confounder reported	
Rajpathak et al. [12]	Male participants of the Health Professionals Follow-up study (HPFS) cohort	Cross-sectional; nested case-control	Levels of toenail selenium among diabetics with or without CVD are lower than in healthy controls **Cross-sectional:** Baseline diabetes vs. healthy controls 0.54-<0.82 µg/g OR = 1 0.83-<0.93 µg/g OR = 0.77 (95% CI 0.53-1.14) 0.94-<1.00 µg/g OR = 0.58 (95% CI 0.39-0.85) 1.01-12.4 µg/g OR = 0.43 (95% CI 0.28-0.66) **Nested case-control:** 0.54-<0.82 µg/g OR = 1 0.83-<0.93 µg/g OR = 0.71 (95% CI 0.39-1.29) 0.94-<1.00 µg/g OR = 0.71 (95% CI 0.40-1.25) 1.01- 12.4 µg/g OR = 0.58 (95% CI 0.29-1.05)	Age Smoking Alcohol intake Hypertension High cholesterol Family history of MI*) Physical activity Body mass index Dietary score Toenail levels of chromium and mercury *): myocardial infarction	
Czernichow et al. [20]	SU.VI.MAX clinical trial on middle aged persons	Clinical trial	Supplementation with antioxidants at nutritional doses had no effect on fasting glucose level In multivariate mixed models, baseline selenium was positively associated with FPG	Age Sex Body mass index Smoking Physical activity Educational level Supplement group Energy intake	Post-hoc analysis Incidence of diabetes not reported

Table 2 (continued)

Reference	Study/Cohort	Design	Results	Confounders considered	Comment
Bleys et al. [9]	Adult participants of the Third National Health and Nutrition Examination Study (NHANES III)	Cross-sectional	Significant risk in the highest category of serum selenium no clear trend in quintiles 2-4 ‹ 111.62 ng/ml OR = 1 111.62-120.17 ng/ml OR = 1.40 (95% CI 0.97-2.00) 120.18-128.25 ng/ml OR = 1.03 (95% CI 0.73-1.47) 128.26-137.65 ng/ml OR = 1.15 (95% CI 0.82-1.62) ≥ 137.66 ng/ml OR = 1.57 (95% CI 1.16-2.13) Spline regression model showed increase in the Odds for diabetes at › 130 ng/ml with plateau at ›150 ng/ml	Age Sex Race/ethnicity Education Family income Postmenopausal status (women) Smoking Serum cotinine Alcohol consumption Physical activity Body mass index C-reactive protein Hypercholesterolemia Serum triglycerides Hypertension Glomerular filtration rate Vitamin/mineral supplement use Intake of β-carotene Vitamin E Serum levels of albumin α-carotene etc.	
Stranges et al. [11]	Participants of the Nutritional Prevention of Cancer (NPC) trial	Clinical trial	Significant increased risk in highest tertile T1: ≤ 105.2 ng/ml HR = 1.13 (95% CI 0.58-2.18) T2: 105.3 to 121.6 ng/ml HR = 1.36 (95% CI 0.60-3.09) T3: › 121.6 ng/ml HR = 2.70 (95% CI 1.30-5.61)	Age Sex Body mass index Smoking status at baseline	Post-hoc analysis; low diabetes numbers in analysis Only few potential confounders considered
He et al. [13]	Participants of the CARDIA Trace Element Study	Cohort	Toenail selenium levels were inversely and borderline significantly associated with incidence of type 2 diabetes. Q1: HR = 1 Q2: HR = 0.91 (95% CI, 0.60 to 1.36) Q3: HR = 0.89 (0.58 to 1.35) Q4: HR = 0.98 (0.65 to 1.50) Q5: HR = 0.59 (0.36 to 0.97)	Age Race Gender Study center Education Body mass index Smoking status Physical activity Family history of diabetes other potential dietary and non-dietary confounders	published only as conference abstract

Table 2 (continued)

Reference	Study/Cohort	Design	Results	Confounders considered	Comment
Laclaustra et al. [10]	Adult participants of the National Health and Nutrition Examination Study (NHANES)	Cross-sectional	Significant risk in the highest category of serum selenium Significant trend ‹ 124 ng/ml OR = 1 124-133 ng/ml OR = 3.18 (95% CI 1.01-9.96) 134-146 ng/ml OR = 3.65 (95% CI 1.31-10.16) ≥ 147 ng/ml OR = 7.64 (95% CI 3.34-17.46) Spline regression model showed increase in odds up to › 130 ng/ml with plateau at >150 ng/ml	Age Sex Race/ethnicity Education Postmenopausal status (women) Smoking Serum cotinine Body mass index Vitamin/mineral supplement use	
Lippman et al. [14]	Participants of the Selenium and Vitamin E Cancer Prevention Trial (SELECT)	Clinical trial	No significant increase in risk Placebo RR = 1 Vitamin E RR = 1.04 (95% CI 0.91-1.18) Selenium RR = 1.07 (95% CI 0.94-1.22) Selenium + Vitamin E RR = 0.97 (95% CI 0.85-1.11)	No; equal distribution of known risk factors across all trial groups	No analysis by selenium level
Akbaraly et al. [22]; *Coudray* et al. [21]	French vascular aging cohort – EVA elderly population	Prospective cohort	Borderline significant lower risk in men in highest tertile; no association among women **Men:** T1: 14-79 ng/ml HR = 1 T3: 94-156 ng/ml HR = 0.50 (95% CI 0.24-1.04) **Women:** T1: 14-79 ng/ml HR = 1 T3: 94-156 ng/ml HR = 1.13 (95% CI 0.55-2.32)	Age Education Alcohol intake Smoking Blood lipids Use of hypertensive or lipid-lowering drugs CVD history Blood pressure Body mass index Oxidative stress markers	No information on selenium supplementation during follow-up; hight rate of attrition
Algotar et al. [15]	Participants of the Watchful Waiting Trial on the effects of selenium supplementation on prostate cancer progression	Clinical trial	No statistically significant difference between either the 200 µg/day (p = .59) or the 800 µg/day (p = .91) and the placebo group Sensitivity analysis among those with all fasting glucose data also showed no effect	Age Race Smoking Body mass index Fasting status Baseline serum glucose Gleason score	High baseline selenium (134.5 ng/ml) level

Table 2 (continued)

Reference	Study/Cohort	Design	Results	Confounders considered	Comment
Stranges et al. [23]	Participants of the ORDET (Hormones and diet in the etiology of breast cancer) study	Cohort	Increased dietary selenium intake associated with increased risk of diabetes; trend significant ‹ 47 µg/day — OR = 1 47.1-53.0 µg/day — OR = 1.42 (95% CI 0.87-2.34) 53.1-58.5 µg/day — OR = 1.43 (95% CI 0.86-2.38) 58.6-65.9 µg/day — OR = 1.65 (95% CI 0.98-2.78) › 65.9 µg/day — OR = 2.39 (95% CI 1.32-4.32) Continuous analysis: odds ratios associated with a 10 µg/d increase in selenium intake were 1.29 (95% CI: 1.10, 1.52) in the fully adjusted model. *"The linearity of the relationship between selenium intake and risk of diabetes was confirmed in spline regression models (not shown)."*	Age Education Menopausal status Body mass index Smoking Alcohol intake Energy intake Saturated/polyunsaturated fatty acids ratio Animal proteins Total carbohydrates Weight change between the baseline and follow-up examinations	
Park et al. [16]	Two U.S. cohorts – nurses and health professionals (NHS and HPFS)	Prospective cohort	Significant, inverse relationship (p trend ‹ 0.01) Males (Females) ‹ 0.719 µg/g (‹0.665) — HR = 1.0 719-‹0.788 µg/g (0.665-‹0.726) — HR = 0.91 (95% CI 0.73-1.14) 0.788-‹0.858 µg/g (0.726-‹0.784) — HR = 0.78 (95% CI 0.62-0.99) 0.858-‹0.950 µg/g (0.784-‹0.859) — HR = 0.72 (95% CI 0.57-0.91) 0.950 ≤ µg/g (0.859 ≤) — HR = 0.76 (95% CI 0.60-0.97)	Age Sex Future case-control status Geographic region Smoking Alcohol intake Physical activity Body mass index Selenium supplement use Multivitamin use Consumption of total energy Ratio of polyunsaturated to saturated fats Trans fat Whole grains Coffee	
Rayman et al. [24]	Participants of the UK PRECISE (PREvention of Cancer by Intervention with SElenium) pilot study	Clinical trial	No diabetogenic effect of a six-month supplementation with selenium In baseline cross-sectional analyses, the fully adjusted geometric mean (GM) of plasma adiponectin was 14% lower (95% CI, 0 to 27%) in the highest than in the lowest quartile of plasma selenium No change in GM plasma adiponectin levels in all four groups after six months supplementation despite significant increase in plasma selenium levels	Sex Study Center	Mean plasma selenium level at baseline 85.5 ng/g

Table 3:
Animal studies related to diabetes endpoints

Reference	Test System	Substance	Exposure	Duration	Diabetes-Related Outcome	Remarks
Pinto et al. [27]	Male pigs	Selenium-enriched yeast	Selenium-adequate (0.17 mg selenkum/kg) or a selenium-supranutritional (0.50 mg selenium/kg; high-selenium) diet.	16 weeks	**LOAEL 0.5 mg Se/kg** Fasting plasma insulin and cholesterol levels were non-significantly increased in the high-Se pigs, whereas fasting glucose concentrations did not differ between the two groups. In skeletal muscle of high-Se pigs, glutathione peroxidase activity was increased, gene expression of forkhead box O1 transcription factor and peroxisomal proliferator-activated receptor-γ coactivator 1α were increased and gene expression of the glycolytic enzyme pyruvate kinase was decreased. In visceral adipose tissue of high-Se pigs, mRNA levels of sterol regulatory element-binding transcription factor 1 were increased, and the phosphorylation of Akt, AMP-activated kinase and mitogen-activated protein kinases was affected.	In conclusion, dietary Se oversupply may affect expression and activity of proteins involved in energy metabolism in major insulin target tissues, though this is probably not sufficient to induce diabetes. Selenium may induce metabolic and molecular alterations, resulting in an increase in lipid turnover and a shift in fuel selection from carbohydrates to lipids in skeletal muscle and visceral adipose tissue.
Zeng et al. [28]	F Wistar rats 67 days old, fed for five weeks, bred and sacrificed on day 14 post-partum Pups fed same diet as respective dam	Selenium-enriched yeast (mainly as selenomethionine)	0, 0.3, 3 mg selenium per kg diet (corn-soy bean selenium-deficient (12 µg selenium/kg) basal diet)	5 weeks + pregnancy + 14 days; Pups for 112 days	No changes during first 5 weeks, but during gestation: **LOAEL 3 mg/kg diet** No changes in body weight, but ↑ body weight gain between GD0-19; ↑ fasting plasma insulin level on GD19; ↑ fasting plasma glucose level on D14PP; → HOMA-IR [1] ↑ from GD19 – D14PP = insulin resistant; No difference on GD0 but on GD19 ↑ blood glucose levels after i.p. glucose or insulin injection (glucose/insulin tolerance test) = hyperinsulinemia and insulin resistance; ↑ plasma triglyceride levels on GD19 = hyperlipidemic effect. Pups: ↑ body weight for first 8 weeks (giant baby syndrome associated with maternal gestational diabetes); on day 112 ↑ fasting plasma glucose; ↑ HOMA-IR; ↑ blood glucose levels after i.p. glucose or insulin injection (glucose/insulin tolerance test) ↓ mRNA and/or protein levels of 6 insulin signal proteins in liver and muscle of dams and/or pups; ↑ GPx1 mRNA/activity in pancreas, liver, and erythrocytes of dams; → moderate gestational diabetes mellitus and postpartum insulin resistance and insulin resistance in pups; linked to gene expression changes of several selenium proteins	Authors noted that potential confounding effects of yeast constituents other than Se cannot be ruled out; Since there was increase in GPx1 activity at highest dose, 0.3 mg selenium/kg diet might be somewhat selenium-deficient

[1] HOMAR-IR: homeostasis model assessment of insulin resistance index

Table 3 (continued)

Reference	Test System	Substance	Exposure	Duration	Diabetes-Related Outcome	Remarks
Labunskyy et al. [29][2]	Male C57BL/6J mice after weaning	Sodium selenite	0, 0.1, 0.4 mg selenium per kg diet (Torula yeast selenium-deficient)	3 months	**LOAEL 0.4 mg/kg diet** Impaired insulin sensitivity (↑ plasma glucose levels after i.p. injection of insulin in overnight fasted mice); Hyperinsulinemia (↑ steady state plasma insulin in fed, but not fasted mice; no significant changes in steady state plasma glucose levels) Liver and kidney extracts had significantly ↑ GPx1 and MsrB activities compared to controls;	0.4 ppm ~ 200 µg/d in humans; 0.1 ppm ~ 55 µg/d in humans; 0.1 ppm Na selenite → max GPx1 expression in mice ↔ 55 µg/d selenium → max GPx1 expression in humans (*Handy et al.* 2009) Expression of stress-related Se proteins ~ insulin sensitivity ↓ Authors suggest that in addition to ↓ H_2O_2 levels, GPx1 overexpression selectively upregulates other Se proteins; Both high as well as low levels of Se protein may lead to diabetes

[2] In a parallel experiment reported in this publication, transgenic mice encoding i6A-mutant Sec (selenium cysteine) tRNA and Wild type (FVB/N) mice were fed standard chow diet. Sec insertion in selenium proteins is decreased by mutant tRNA, resulting in lower selenium protein expression. Expression and activities of GPx1, MsrB1 and others were decreased. The same parameters as measured for the selenium-supplemented mice were measured and all effects seen were more pronounced in transgenic mice compared with their wild type (↑ plasma glucose levels after i.p. injection of insulin in overnight fasted mice; ↑ steady state plasma insulin in fed, but not fasted mice; ↑ steady state plasma glucose level).

Table 4:
Percent baseline plasma glucose following insulin challenge

Selenium in diet (ppm)	Minutes after insulin challenge			
	30	60	120	240
0.1 (Normal diet)	69.41 (7.57)	52.47 (9.37)	61.31 (13.97)	109.08 (33.73)
0.4	89.92 (20.94)	82.75 (20.83)	111.19 (16.48)	96.45 (26.12)

Labunskyy et al. [29|

Table 5:
Characteristics of epidemiological studies on cancer and selenium

Reference	Study/cohort	Study year	Country	Design	Size	Exposure determination	Outcome definition and determination
Willett et al. [121]	Participants of the Hypertension Detection Follow-up program, 30 to 69 years	1973/1974 to 1979	US	Nested case- control	With serum sample available N = 4,480	Serum selenium	any cancer incidence
Clark et al. [122]	Person at high risk of non-melanoma skin cancer	not reported	US	Cohort	N = 177	Plasma selenium	non-melanoma skin cancer incidence
Salonen et al. [123]	Random sample of two Finnish provinces (North Karelia Project)	1972 to 1978	Finland	Nested case-control	Free of cancer, age 31 to 59 N = 8,113	Serum selenium	any cancer incidence
Salonen et al. [124]	Random sample of two Finnish provinces (North Karelia Project)	1977 to 1980	Finland	Nested case-control	Free of cancer, age 30 to 64 N = 12,155	Serum selenium	any cancer mortality
Peleg et al. [125]	Residents of Evans county, 15 years and older	1967 to 1981	US	Nested case-control	Free of cancer at baseline and during first two years of follow-up	Serum selenium	any cancer incidence
Menkes et al. [126] *Helzlsouer* et al. [57] *Burney* et al. [127] *Zheng* et al. [128] *Batieha* et al. [129] *Ko* [130], as cited in *Dennert* et al. [55] *Breslow* et al. [131] *Helzlsouer* et al. [132]	Inhabitants of Washington county/ Maryland (CLUE 1 Cohort)	1974 to 1983	US	Nested case-control	Free of cancer at baseline N = 25,804	Serum selenium	lung cancer (*Menkes*) bladder cancer (*Helzlsouer* 1989) pancreatic cancer (*Burney*) oral/pharyngeal (*Zheng*) cervical (*Batieha*) colon cancer (*Ko*) melanoma, basal cell carcinoma (*Breslow*) ovarian cancer (*Helzlsouer* 1996)
Fex et al. [133]	Residents of Malmo, age 46 to 48	1975 to 1981	Sweden	Nested case-control	Prevalent cases included N = 7,935	Plasma selenium	any cancer mortality
Kok et al. [134]	Male inhabitants of Zoetermeer, age 5 years and older (EPOZ cohort)	1975 to 1983	Netherlands	Nested case-control	N = 10,532	Serum selenium	any cancer mortality
Kromhout [135]	Random sample of male population, age 40 to 50 years, in Zutphen	1960 to 1985	Netherlands	Cohort	N = 878	Selenium intake (questionnaire)	lung cancer mortality
Nomura et al. [136]	Male participants of the Honolulu Heart program, Japanese ancestry, age between 50 and 75	1971/1975 to 1982	US	Nested case-control	N = 6,860	Serum selenium	any cancer (as sum of below) stomach, rectal, lung, colon, bladder, incidence

Table 5 (continued)

Reference	Study/cohort	Study year	Country	Design	Size	Exposure determination	Outcome definition and determination
Virtamo et al. [137]	Male inhabitants of rural Finland, age 55 to 74 years	1974 to 1983	Finland	Cohort	Serum sample available, prevalent cases and those within first year of follow-up excluded N = 1,110	Serum selenium	any cancer incidence
Van Noord et al. [138; 139]	Femals inhabitants of Utrecht, pre-menopausal, age 42 to 52 years (DOM study)	1983 to 1986	Netherlands	Nested case-control	N = 8,760	Toenail selenium	breast cancer incidence
Ringstad et al. [140]	Inhabitants of Tromso with blood sample in 1979 (Tromso Heart Study II)	1979 to 1985	Norway	Nested case-control	N = 9,364	Serum selenium	any cancer incidence
Coates [141], *Coates* et al. [142]	Employees of two Seattle companies	1972 to 1984	US	Nested case-control	N = 6,164	Serum and plasma selenium	any cancer, gastrointestinal, breast, prostate, haematological, cervical, lung, other incidence
Glattre et al. [143]	Norwegian Cancer Society Janus serum bank	1972 to 1985	Norway	Nested case-control	N = 100,000	Serum selenium	thyorid cancer incidence
Knekt et al. [144] *Knekt* et al. [145] *Hakama* et al. [146] *Knekt* et al. [147] *Knekt* et al. [148] *Knekt* et al. [149]	Participants of the Social Insurance Institution's Mobile Clinic Health Examination Survey	1968/1972 to 1980 to 1977 to 1986 to 1980 1973 to 1976 1973 to 1991	Finland	Cohort/Nested case-control	N = 39,268 N = 36,265 not reported N = 4,538 (male) N = 1,896 (female) N = 9,101	Serum selenium (dietary history)	any cancer stomach, colon and rectal, lung, prostate, urinary tract, pancreatic, breast, gynaecological, basal cell, other oesophageal and stomach, colon and rectal any cancer lung, breast, stomach, prostate lung ovarian lung incidence
Overvad et al. [150]	Female participants of the Channel Island Cohort older than 35 years	1967/76 to 1985	Channel Islands	Cohort	N = 5,162	Plasma selenium	breast cancer incidence
Yu et al. [151] *Li* [152], as cited in *Dennert* et al. [55] *Yu* et al. [153]	Residents in Qidong province	2 years	China	Clinical trial	N = 2,474 (3,849) first-degree relatives within three generations of families with 2 or more cases of liver cancer during the 1972 to 1985	200 µg selenium as selenised yeast/day	primary liver cancer

Table 5 (continued)

Reference	Study/cohort	Study year	Country	Design	Size	Exposure determination	Outcome definition and determination
Hagmar et al. [154], as cited in *Dennert* et al. [55]	Baltic Sea fishermen	1944 to 1987	Sweden	Cohort	N = 1,360	Intake (questionnaire, small sample) Plasma selenium (small sample)	various sites
Combs et al. [155]	Male and female participants of the Nutritional Prevention of Cancer Trial (NPCT)	1983/1991 to (2 years follow-up)	US	Cohort	N = 1,239 with history of 2 or more squamous cell or basal cell skin cancer	Plasma selenium Intervention: 200 µg selenium as 500 mg selenium yeast tablets/day	squamous cell skin cancer incidence
van den Brandt et al. [156; 157] *van den Brandt* et al. [158] *Zeegers* et al. [58] *van den Brandt* et al. [159]	Participants of the Netherlands Cohort Study (NLCS)	1986 to 1989 to 1989 to 1992	Netherlands	Cohort	N = 120,852, 55 to 69 years without history of cancer N = 62, 573 (female) N = 120,852 N = 58, 279 (male)	Toenail selenium	stomach, colon, rectal, lung breast bladder prostate cancer incidence
Kabuto et al. [160]	Male and female participants of the Adult Health Study Hiroshima and Nagasaki	1960 to 1983	Japan	Nested case-control	N = 20,000	Serum selenium (1970 to 1972)	lung, stomach incidence
Garland et al. [161]	Female participants of the Nurses' Health Study (NHS)	1976 to 1986	US	Nested case-control	N = 62,641 with no history of cancer at baseline and with toenail sample in 1982	Toenail selenium (1982)	any cancer colon and rectal, melanoma, ovarian, lung, uterine, other incidence
Clark et al. [59] *Duffield-Lillico* et al. [56]	Male and female participants of the Nutritional Prevention of Cancer Trial (NPCT)	1983/1991 to 1996	US	Clinical trial	N = 1,312 with history of 2 or more squamous cell or basal cell skin cancer	Plasma selenium Intervention: 200 µg selenium as 500 mg selenium yeast tablets/day	squamous and basal cell skin cancer secondary: any cancer, lung, prostate, colorectal, head and neck, bladder, oesophageal, breast, melanoma, haematologic incidence
Comstock et al. [162]	Male and female participants of the CLUE I and II Cohort among residents of Washington County	1974 or 1989 to 1993	US	Nested case-control	Cases N = 258	Plasma/serum selenium	lung cancer incidence
Karagas et al. [163]	Male and female articipants of the Skin Cancer Prevention Study (clinical trial)	1983/86 to 1989	US	Nested case-control	N = 1,805 at least one BCC or SCC before study entry	Plasma selenium	squamous cell skin cancer

Table 5 (continued)

Reference	Study/cohort	Study year	Country	Design	Size	Exposure determination	Outcome definition and determination
Yu et al. [164]	Recruitment through screening of a village	1987 to 1994	China	Clinical trial	N = 226	Intervention: 200 µg selenium as selenised yeast/day for 4 years	primary liver cancer incidence
Dorgan et al. [165]	Female volunteers with serum available at Breast Cancer Serum Bank in Missouri	1977/1988 to 1989 (majority until 1982/83)	US	Nested case-control	N = 6,426 no history of cancer at baseline	Serum selenium	breast cancer incidence
Hartman et al. [166]	Male participants, age 50 to 69, of the ATBC study	1985/88 to 1993	Finland	Cohort	N = 29,133 no history of cancer at baseline, smokers	Intake (questionnaire)	prostate cancer incidence
Yoshizawa et al. [167]	Male participants of the Health Professionals Follow-Up Study (HPFS)	1986/87 to 1994	US	Nested case-control	N = 33,737	Toenail selenium	prostate cancer incidence
Yu et al. [168]	Male, 30 to 65 years recruited in two clinics in Taipei	1984/92 to 1996	Taiwan	Nested case-control	N = 4,841	Plasma selenium	primary liver cancer incidence
Helzlsouer et al. [169]	Male participants of the CLUE II Cohort among residents of Washington County	1989 to 1996	US	Nested case-control	N = 10,456	Toenail selenium	prostate cancer incidence
Li et al. [170]	Male residents of Qidong province, age 20 to 65 years	to 1999	China	Clinical trial	N = 2,065	Intervention: 0.5 mg sodium selenite/day for 3 years	primary liver cancer incidence
Nomura et al. [171]	Male participants of the Honolulu Heart program, Japanese ancestry, age between 50 and 75 and brothers of the participants	1971/77 to 1995	US	Nested case-control	N = 9,345 no cancer diagnosis at baseline	Serum selenium	prostate cancer incidence
Persson-Mosches et al. [172]	Male participants of the Malmö Preventive Program, age 46 to 48 years	1974/82 to 1988	Sweden	Nested case-control	N ~ 9,500	Plasma selenium	any cancer, gastrointestinal, respiratory tract, urinary tract, other
Ratnasinghe et al. [173]	Tin miners with 10 or more years underground/smelting and older 34 years	1992/97 to 1997	China	Nested case-control	N = 9,143 no history of cancer at baseline	Serum selenium	lung cancer incidence
Brooks et al. [174]	Male participants of the Baltimore Longitudinal Study of Aging	1991 to	US	Nested case-control	N = 1,555	Plasma selenium	prostate cancer incidence
Goodman et al. [175]	Male and female color members of the Caret (Carotene and Retinol Efficacy Trial)	1988/94 to 98	US	Nested case-control	N = 18,314	Serum selenium	lung cancer incidence
Kilander et al. [176], as cited in *Dennert* et al. [55]	Men of Uppsala, age 50 years	1970/73 to 1995	Sweden	Cohort	N = 2,301 those died within the first 2 years of follow-up excluded	Serum selenium	any cancer mortality
Davies et al. [177]	Male participants of the EPIC study	1992/2000 to 1999/2003	UK	Nested case-control	Cases N = 123	Plasma selenium	non-melanoma skin cancer Incidence

Table 5 (continued)

Reference	Study/cohort	Study year	Country	Design	Size	Exposure determination	Outcome definition and determination
Michaud et al. [178]	Male participants of the ATBC study, 50 to 69 years	1958/88 to 1993	Finland	Nested case-control	N = 29,133 no history of cancer other non-melanoma skin cancer at baseline	Toenail selenium	bladder cancer
Hartmann et al. [179]					Cases N = 250		lung cancer Incidence
Ujiie and *Kikuchi* [180]	Hospital patients in Miyagi in 1993	1993 to 1998	Japan	Cohort	N = 2,312 Cases N = 73 no cancer diagnosed at baseline or within 6 months of follow-up	Serum selenium	any cancer incidence
Kornitzer et al. [181]	Male participants of the Belgian Interuniversity Study on Nutrition and Health, 25 to 74 years	1980/84 to 1990	Belgium	Nested case-control	Cases N = 193	Serum selenium	any cancer mortality
Li et al. [182]	Male participants of the Physicians' Health Study	1982 to 1995	US	Nested case-control	N = 14,916 no history of cancer at baseline	Plasma selenium	prostate cancer incidence
Wei et al. [183]	Healthy controls of the General Population Trial Linxian, 40 to 69 years	1986 to 2001	China	Nested case-control	N = 1,103	Serum selenium	oesophageal cancer, stomach, cardia cancer stomach, non-cardia cancer other mortality
Akbaraly et al. [184]	Participants of the EVA study, 59 to 71 years	1991/93 to 2001	France	Cohort	N = 1,389	Plasma selenium	any cancer mortality
Michaud et al. [185]	Participants of the HPFS and the NHS study	1983/87 to 2000	US	Nested case-control	N = 101,950 no history of cancer at baseline Cases N = 337	Toenail selenium	bladder cancer incidence
McNaughton et al. [186]	Participants of the Nambour Skin Cancer study, 20 to 69 years	1992/96 to 2001	Australia	Nested case-control Cohort	N~1,000 no history of SCC at baseline Cases N = 90	Serum selenium	basal cell carcinoma of the skin (BCC) squamous cell carcinoma of the skin (SCC) Incidence
Heinen et al. [187]		to 2004			Cases BCC 149, SCC 116		BCC and SCC
van der Pols et al. [188]		to 2004			Cases BCC 77, SCC 59		BCC and SCC

Table 5 (continued)

Reference	Study/cohort	Study year	Country	Design	Size	Exposure determination	Outcome definition and determination
Sakoda et al. [189]	Inhabitants of Haiman with Chinese origin	1993 to 2000	China	Nested case-control	N = 41,563 with toenail sample after 2000 Cases N = 166	Toenail selenium	primary liver cancer mortality
Kune and *Watson* [190]	Participants of the Melbourne Colorectal Cancer Study	1980 to 1981	Australia	Case-control	Cases/controls N = 715/727	Dietary intake (questionnaire)	colorectal cancer incidence
Le Marchand et al. [191]	Caucasian residents of Oahu, Hawaii, 18 to 79 years	1986 to 1992	US	Case-control	Cases N = 278	Plasma and toenail selenium	melanoma Prevalence/Incidence
Cui et al. [192]	Females with a diagnosis of benign breast disease between 1970 and 1994 at Kaiser Permanente Northwest	1970 to 1994	US	Nested case-control	Cases N = 252 diagnosed with breast cancer before, or within 1 year of benign breast biopsy were excluded	Elemental levels in breast tissue using X-ray fluorescence spectroscopy	breast cancer incidence
Peters et al. [193]	White, non-hispanic participants of the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial, 55 to 74 years	1993/2001 to 2001	US	Nested case-control	N = 26,975 Cases N = 724	Serum selenium	prostate cancer Incidence
Allen et al. [194]	Male participants of the EPIC study	1992/2000 to 1999/2003	Europe	Nested case-control	N = 130,000 Cases N = 959	Plasma selenium	prostate cancer Incidence
Bleys et al. [195]	Participants of the NHANES III study, 20 to 90 years	1988/94 to 2000	US	Cohort	N = 13,887 Cases N = 457	Serum selenium	any cancer Mortality
Dong et al. [196]	Participants of the Seattle Barrett's Esophagus Program	1995 to 2004	US	Cohort	N = 339 with Barrett's oesophagus cases N = 37	Supplemental intake (questionnaire)	oesophageal adenocarcinoma Incidence
Peters et al. [197]	White participants of the Vitamins And Lifestyle (VITAL) study in Washington state, 50 to 76 years	2000/02 to 2004	US	Cohort	N = 35,242 (males) Cases N = 818	supplemental intake (questionnaire)	prostate cancer
Asgari et al. [198]		to 2006			N = 69,671 Cases N = 461		melanoma incidence
Reid et al. [199]	Participants of the NPCT trial	1989/92 to 1996	US	Clinical trial	N = 423 with prior non-melanoma skin cancer	Supplementation with 400 µg selenium as yeast tablets/day	basal and squamous cell carcinoma of the skin incidence
Thomson et al. [200]	Female participants of the Women's Health Initiative (WHI) trial and observational study, 50 to 79 years	to 2004	US	Cohort	N = 133,614 Cases N = 451	Supplemental intake (questionnaire)	ovarian cancer incidence
Connelly-Frost et al. [201]	Participants of the North Carolina Colon Cancer Study (NCCCS)	1996 to 2000	US	Case-control	Cases N = 1,691	Serum selenium	colon cancer incidence

Table 5 (continued)

Reference	Study/cohort	Study year	Country	Design	Size	Exposure determination	Outcome definition and determination
Epplein et al. [202] *Gill* et al. [203]	Participants of the Multiethnic Cohort	1993/96 to 2006	US	Nested case-control	N = 67,594 with blood sample before cancer diagnosis Cases N = 207 N = 29,009 (male) Cases N = 467	Serum selenium	lung cancer prostate cancer incidence
Lippmann et al. [14]	Participants of the Selenium and Vitamin E Cancer Prevention Trial (SELECT)	2001 to 2009	US, Canada, Puerto Rico	Clinical trial	35,533 healthy men older than 50 years (median age › 62) 4-group trial: placebo vitamin E + placebo selenium + placebo selenium + vitamin E	Serum selenium Supplementation with 200 µg Se/day (from L-selenomethionine)	prostate cancer any cancer, lung, colorectal cancer incidence
Wallace et al. [204]	Cancer registry in New Hampshire, aged 25 to 74 years	1994 to 2001	US	Case-control	Cases/controls 857/1,191	toenail selenium	bladder cancer incidence
Thompson et al. [205]	Participants of the Iowa Women's Health Study, aged 55 to 69 years	1986 to 2005	US	Cohort	N = 35,159	dietary intake (questionnaire)	non-Hodgkin lymphoma incidence

Table 6:
Available Animal Studies on Cancer and Selenium (oral exposure)

Citation	Cited in ATSDR 2003 [2]	Cited in MAK 1999/2011 [8; 77]	Cited in IRIS 1993 [76]	Cited in IARC 1975 [1]
NCI [63] (rats)	yes	yes	no	n/a
NCI [63] (mice)	yes	yes	no	n/a
Innes et al. [70]; NCI [206]	yes	no	no	yes
Schroeder and *Mitchener* [66]	yes	no	yes	yes
Schroeder and *Mitchener* [67]	yes	yes	yes	yes
Harr et al. [64]; *Tinsley* et al. [65]	yes	yes	yes	yes
Volgarev and *Tscherkes* [68], as cited in ATSDR [2]	yes	no	no	no
Tscherkes et al. [69], as cited in *Harr* et al. [64]	no	no	no	no
Seifter et al. [72], as cited in *Bielschowsky* et al. [73]	no	no	no	no
Seifter et al. [71]	no	no	no	no
Nelson et al. [74]; *Fitzhugh* et al. [207], as cited in ATSDR [2]	yes	yes	yes	yes

Table 7a:
Cancer studies in healthy animals

<table>
<tr><th>Reference</th><th>Test System</th><th>Substance</th><th>Exposure</th><th>Duration</th><th>Tumor Incidence/Cancer-Related Results</th><th>Remarks/Conclusion</th></tr>
<tr>
<td>National Cancer Institute [63]</td>
<td>Rats
Mice</td>
<td>SeS
(MW 111.045 g/mol)</td>
<td>Oral gavage
3,15 mg/kg/day
20, 100 mg/kg/day
As SeS</td>
<td>104 weeks</td>
<td>
<table>
<tr><th colspan="4">Tumor incidence (M/F)</th></tr>
<tr><th></th><th colspan="3">Dose (mg/kg/day SeS)</th></tr>
<tr><th>Rats</th><th>Controls</th><th>3</th><th>15</th></tr>
<tr><td>Hepato-cellular carcinomas</td><td>1/50/
0/50</td><td>0/50/
0/50</td><td>15/49/
21/50</td></tr>
<tr><th>Mice</th><th>Controls</th><th>20</th><th>100</th></tr>
<tr><td>Hepato-cellular carcinomas & adenomas</td><td>15/50/
0/49</td><td>14/50/
2/50</td><td>23/50/
25/49</td></tr>
</table>
</td>
<td>Statistically significant ↑ in hepato-cellular carcinomas and adenomas in rats

Statisticalli significant ↑ hepatic carcinomas and adenomas, as well as alveolar/bronchiolar carcinomas and adenomas, in female mice
<table>
<tr><th colspan="3">Hepatocellular Carcinomas and/or Adenomas</th></tr>
<tr><td rowspan="2">Species</td><td colspan="2">Se dose (mg/kg/day)</td></tr>
<tr><td>NOAEL</td><td>LOAEL</td></tr>
<tr><td>Rats</td><td>2.1</td><td>10.07</td></tr>
<tr><td>Mice</td><td>14.2</td><td>71</td></tr>
</table>
</td>
</tr>
<tr>
<td>Schroeder and Mitchener [66]</td>
<td>White Swiss CD mice
(50/sex/group)</td>
<td>sodium selenite or sodium selenate</td>
<td>Drinking water
3 mg selenium/L
as either sodium selenite or sodium selenate
(+ 1 ppm or 5 ppm Cr, respectively)
(0.31 to 0.34 mg selenium/kg/day for males and 0.42 mg selenium/kg/day for females)</td>
<td>lifetime</td>
<td>
<table>
<tr><th>Group</th><th>Tumor incidence</th></tr>
<tr><td>Controls 180 autopsied</td><td>23/119 sectioned (19%):
10/119 (8%) or 10/23 (43%) of tumors malignant;
2 lymphoma-leukemia;
7 lung carcinoma, 1 unknown origin, 13 benign tumors of breast, ovary, others</td></tr>
<tr><td>Se 3 ppm,
176 autopsied</td><td>13/88 (15%) sectioned, all malignant: 8 lymphoma-leukemia, 4 papillary or alveolo-genic adenocarcinoma of the lung, 1 osteosarcoma</td></tr>
</table>
Selenite ↑ body weight of M, but body weight ↓ of F, selenite › selenate; both forms ↑ body weight loss in older animals
Body weights of selenate-treated animals were comparable to controls.
Longevity in males fed selenate was increased compared with controls. Longevity in females fed selenate increased, but longevity in females fed selenite decreased compared with controls.
</td>
<td>Malignant tumor incidence 43% in controls vs. 100% with Se, but this was not significant.
Selenate ↑ lifetime, selenite ↓ lifetime
In this study, only 88 out of 211 selenium-treated animals and 119 out of 209 control animals were examined histologically</td>
</tr>
</table>

Table 7a (continued)

<table>
<tr><th>Reference</th><th>Test System</th><th>Substance</th><th>Exposure</th><th>Duration</th><th>Tumor Incidence/Cancer-Related Results</th><th>Remarks/Conclusion</th></tr>
<tr>
<td>Schroeder and Mitchener [67]</td>
<td>Long-Evans rats (approximately 50/sex/group at study initiation)
105 controls</td>
<td>Sodium selenite or sodium selenate</td>
<td>Drinking water
2 ppm Se* for 1 year, then 3 ppm for the remainder of the study
After 58 days M rats on selenate were transferred to selenite (0.28 to 0.42 mg selenium/kg/day)

* IARC [1] noted that this is equivalent to 4.5 ppm in diet</td>
<td>Lifetime (~36 months, although one selenate-treated female lived for 5 years)</td>
<td>Selenite produced 50% mortality in males by 58 days. This group was changed to 2 ppm selenate; no tumors after 596 days in surviving rats;
Selenite produced 50% mortality in females by 348 days; selenite- treated females were sacrificed at 23 months due to high mortality.
Survival of rats receiving selenate was comparable to controls and median lifespan was increased by › 100 days.
Statistically significant increase in incidence of all tumors and malignant tumors ↑

<table>
<tr><th rowspan="2">Endpoint</th><th colspan="3">Tumor incidence</th></tr>
<tr><th>Controls</th><th>Selenate</th><th>Selenite</th></tr>
<tr><td>Total tumors</td><td>20/65 (30.8%)</td><td>30/48 (62.5%)</td><td>4/32 (12.5%)</td></tr>
<tr><td>Malignant tumors</td><td>11/65 (16.9%)</td><td>20/48 (41.7%)</td><td>4/32 (12.5%)</td></tr>
<tr><td>Day of earliest tumor</td><td>833 (M), 633 (F)</td><td>344 (M), 633 (F)</td><td></td></tr>
</table>

No difference in body weights of males compared to controls. Body weights of females fed selenate › controls at 24 and 36 months; body weights of females fed selenite were ‹ controls at all times but 18 months.</td>
<td>IARC [1] noted “Although there is a statistical difference in the incidence of all tumours and that of malignant tumours between control and selenate-treated groups, an evaluation of these results was not possible because not all autopsied animals were examined histologically and because treated animals lived longer than controls (the average lifespan of control males and females was 813 and 814 days and that of treated animals 847 and 929 days, respectively).”
ATSDR [2] noted “Analysis of the incidence of tumors among animals with equal longevities indicates that the incidence of tumors in the selenate-treated rats was not significantly different from that in the controls.”
The shortened survival time of the selenite groups was thought to be responsible for the small number of tumors. This study is considered inadequate because only the heart, lung, liver, kidney and spleen tissues from animals necropsied were examined histologically, and an increase in longevity was observed in selenate-treated female rats.
The treatment of the control group was not discussed. Not all autopsied animals were examined histologically.;
High mortality in all groups occurred as a result of a virulent pneumonia epidemic that occurred during the study.</td>
</tr>
</table>

Table 7a (continued)

<table>
<tr><th>Reference</th><th>Test System</th><th>Substance</th><th>Exposure</th><th>Duration</th><th>Tumor Incidence/Cancer-Related Results</th><th>Remarks/Conclusion</th></tr>
<tr><td>Harr et al. [64];
Tinsley at al. [65]
- NCI study</td><td>M/F Wistar rats</td><td>Sodium selenate or sodium selenite</td><td>Diet
0.5, 2, 4, 6, 8, 16 Se ppm
(different experimental diets + different amounts of casein (12 or 22%) + Se or commercial diets, incl with added Se 4 to 16 ppm)
Positive control: AAF (hepato-carcinogen)

max 0.8 mg selenium/kg/day
(authors use different intake levels)</td><td>lifetime</td><td>Mortality very high in 16 ppm group and therefore that dose was terminated. ≥4 ppm ↑↑ mortality ≈ 0.5 mg/kg/day – death due to acute toxic hepatitis ‹ 100 days
Neoplasia: 20 non-AAF related neoplastic lesions were randomly distributed over experimental groups: 9 in Se-experimental diet-treated (9/738 autopsied = 1.2%), 11 in controls (11/308 = 3.6%), none of those were hepatic (positive control AAF: 26 hepatic carcinomas)
Other liver lesions: Hepatic hyperplasia:
50 in situ hepatic abnormal lesions in other rats: positive control AAF: 10/59 autopsied (17%)
controls with no Se-added diets, commercial diets, incl those with Se added, or experimental diets of 0.5 ppm Se: 0/448 autopsied (0%)
experimental diets with 2-8 ppm Se: 40/590 autopsied (7%):

<table><tr><th rowspan="2">Se (ppm)</th><th colspan="3">In Situ Hepatic Lesions</th></tr><tr><th>Total (%)</th><th>Grade 1</th><th>Grade 2</th></tr><tr><td>0.5</td><td>0</td><td>0</td><td>0</td></tr><tr><td>2</td><td>4/88 (5)</td><td>3</td><td>1</td></tr><tr><td>Up to 4</td><td>13/165 (8)</td><td>10</td><td>3</td></tr><tr><td>6</td><td>2/29 (7)</td><td>1</td><td>1</td></tr><tr><td>Up to 8</td><td>9/181 (5)</td><td>6</td><td>3</td></tr></table></td><td>Out of 1,437 experimental animals, 1,126 were necropsied.
Authors noted that 0.5 mg/kg body weight/day [4 ppm] seems to be the threshold level for toxicity and reduced lifespan.
Authors noted that in situ/ hyperplastic liver lesions did not regress when added Se was removed from diet; high cellular turn-over suggests autonomy.
2-3 fold resistance to Se toxicity with commercial diet vs. experimental diet; ↑ protein in diet was protective
Toxicity: Selenate › selenite

<table><tr><th colspan="4">In Situ Hepatic Lesions</th></tr><tr><th colspan="2">Se in diet (ppm)</th><th colspan="2">Se dose (approximate, mg/kg/day)</th></tr><tr><th>NOAEL</th><th>LOAEL</th><th>NOAEL</th><th>LOAEL</th></tr><tr><td>0.5</td><td>2</td><td>0.05</td><td>0.2</td></tr></table>
34 different groups – different diets + different Se concentrations and compounds complicate evaluation of results
High mortality starting at 4 ppm Se may have prevented observation of late developing cancers.</td></tr>
</table>

Table 7a (continued)

<table>
<tr><th>Reference</th><th>Test System</th><th>Substance</th><th>Exposure</th><th>Duration</th><th>Tumor Incidence/Cancer-Related Results</th><th>Remarks/Conclusion</th></tr>
<tr><td>Volgarev and Tscherkes [68], as cited in ATSDR [2]</td><td>Male rats</td><td>Sodium selenate</td><td>Diet
1) 0.34 mg selenium/kg/day
2) 0.34 mg selenium/kg/day for 6 months, followed by 0.68 mg/kg/day until death
3) 0.34 mg selenium/kg/day</td><td>1) › 18 months
2) 6 months + until death
3) 26 months</td><td>1) Tumors (primarily liver) in 10/23 rats, first tumors appeared after 18 months of selenium administration, by which time, 43% (of 40 rats) of the animals had already died
2) Tumors in 3/16 rats
3) No tumors in 200 rats, but very high mortality among these rats, survival time was 10 months shorter than among the similarly fed animals in the first experiment.</td><td>High mortality, tumors appeared mostly late (› 18 months)
<table><tr><th colspan="4">Liver Tumors</th></tr><tr><th colspan="2">Se in diet (ppm)</th><th colspan="2">Se dose (approximate, mg/kg/day)</th></tr><tr><th>NOAEL</th><th>LOAEL</th><th>NOAEL</th><th>LOAEL</th></tr><tr><td>NI</td><td>NI</td><td>NI</td><td>0.34</td></tr></table>
No dedicated controls, but the authors noted that an additional 200 male rats were maintained in their laboratory during these experiments and fed stock rations. The life spans of these animals exceeded those used in the experiments and no tumors were found at autopsy.</td></tr>
<tr><td>Tscherkes et al. [69], as cited in Harr et al. [64] [original in Russian]</td><td>Hetero-zygous rats
N = 40</td><td>Sodium selenate</td><td>Diet
4.3 ppm Se</td><td>Up to 32 months</td><td>23/40 lived › 18 months:
hepatic carcinomas (2 metastasized to lung) in 3/23, 3 hepatic adenomas, 4 considered precancerous [unclear description]</td><td>Criteria of neoplasia included uneven basophilia, preserved architecture, variation in size of cells and nuclei, and fatty degeneration
No information on controls
<table><tr><th colspan="4">Liver Tumors</th></tr><tr><th colspan="2">Se in diet (ppm)</th><th colspan="2">Se dose (approximate, mg/kg/day)</th></tr><tr><th>NOAEL</th><th>LOAEL</th><th>NOAEL</th><th>LOAEL</th></tr><tr><td>NI</td><td>4.3</td><td>NI</td><td>0.22</td></tr></table></td></tr>
</table>

Table 7a (continued)

<table>
<tr><th>Reference</th><th>Test System</th><th>Substance</th><th>Exposure</th><th>Duration</th><th>Tumor Incidence/Cancer-Related Results</th><th>Remarks/Conclusion</th></tr>
<tr>
<td>Innes et al. [70]; National Cancer Institute [206]</td>
<td>Mice
C57BL/6 x C3H/Anf)F1 (strain X);
C57BL/6 x AKR)F1 (strain Y)</td>
<td>Ethyl selenac (Selenium diethyl-dithiocarbamate; MW 672.0384 g/mol)</td>
<td>Oral gavage, then diet ethyl selenac 10 mg/kg body weight/day by gavage on days 7 to 28 of age, after day 28 to 26 ppm in diet vehicle control 0.5% gelatin</td>
<td>81 to 82 weeks (starting age 7 days 82 to 83 weeks)</td>
<td>
<table>
<tr><th>Tumor</th><th></th><th colspan="2">C</th><th colspan="2">Se</th></tr>
<tr><th>Strain</th><th></th><th>x</th><th>y</th><th>x</th><th>y</th></tr>
<tr><td>necropsied</td><td>M
F</td><td>16
16</td><td>18
17</td><td>18
17</td><td>17
17</td></tr>
<tr><td>hepatomas</td><td>M
F</td><td>0
0</td><td>1
0</td><td>12
3</td><td>3
0</td></tr>
<tr><td>pulmonary</td><td>M
F</td><td>0
0</td><td>2
1</td><td>0
0</td><td>3
1</td></tr>
<tr><td>lymphomas</td><td>M
F</td><td>0
0</td><td>0
1</td><td>3
2</td><td>1
3</td></tr>
<tr><td>total</td><td>M
F</td><td>0
0</td><td>3
2</td><td>16
6</td><td>5
4</td></tr>
</table>
</td>
<td>MTD given, starting age 7 days
Diagnostic criteria: Hepatomas = liver tumors that are not metastasized (but not equal benign); hepatoma incidence significant ↑ in strain x
authors noted: incidence of lymphoma in some subgroups of mice treated with ethyl selenac were significantly increased over negative controls
<table>
<tr><th colspan="4">In Situ Liver Lesions</th></tr>
<tr><th colspan="2">Se in diet (ppm)</th><th colspan="2">Se dose (approximate, mg/kg/day)</th></tr>
<tr><th>NOAEL</th><th>LOAEL</th><th>NOAEL</th><th>LOAEL</th></tr>
<tr><td>control</td><td>3.0</td><td>control</td><td>1.2 gavage -0.3</td></tr>
</table>
IARC [1] noted that tumors might have been due to thiocarbamate part not Se.
</td>
</tr>
<tr>
<td>Seifter et al. [72], as cited in Bielschowsky et al. [73]</td>
<td>Information not available</td>
<td>Bis-4-acetamino-phenyl-selenium dihydroxide</td>
<td>Diet
‹ 0.05%</td>
<td>1 to 2 years</td>
<td></td>
<td>“When smaller [than in Seifter et al. 1946 study] amounts were fed over periods of 1-2 years the degree of hyperplasia observed was rather mild and limited to the interior of the gland; only one adenoma was found. Benign liver tumors appeared in these rats, suggestive of a direct carcinogenic action of the compound (Seifter, Ehrich and Hudyma, 1949).”</td>
</tr>
</table>

Table 7a (continued)

<table>
<tr><th>Reference</th><th>Test System</th><th>Substance</th><th>Exposure</th><th>Duration</th><th>Tumor Incidence/Cancer-Related Results</th><th>Remarks/Conclusion</th></tr>
<tr><td>Seifter et al. [71]</td><td>1) white rats (N = 16)
2) white rats (N = 8)</td><td>Bis-4-acetamino-phenyl-selenium dihydroxide (MW 248.16 g/mol)</td><td>Diet
1) 0.05 to 0.1%
2) 0.05%</td><td>1) 10 days
2) 105 days</td><td>1) increased size, hyperplasia, loss of colloid in thyroid glands
2) multiple adenoma of thyroid glands & adenomatous hyperplasia of the liver</td><td>Authors noted goitrogenic action of Se
<table>
<tr><th colspan="4">Adenomas of Thyroid Glands</th></tr>
<tr><td colspan="2">Se in diet (ppm)</td><td colspan="2">Se dose (approximate, mg/kg/day)</td></tr>
<tr><th>NOAEL</th><th>LOAEL</th><th>NOAEL</th><th>LOAEL</th></tr>
<tr><td>NI</td><td>0.05</td><td>NI</td><td>6.36</td></tr>
</table></td></tr>
</table>

Table 7a (continued)

<table>
<tr><th>Reference</th><th>Test System</th><th>Substance</th><th>Exposure</th><th>Duration</th><th>Tumor Incidence/Cancer-Related Results</th><th>Remarks/Conclusion</th></tr>
<tr>
<td>Nelson et al. [74], Fitzhugh et al. [207], as cited in [2]</td>
<td>Female inbred Osborne-Mendel rats 18/group</td>
<td>Naturally seleniferous corn or wheat diets containing Se or added as mixed inorganic selenide (ammonium potassium selenide & ammonium potassium sulfide)</td>
<td>Diet
5, 7, or 10 ppm Se (0.25, 0.35, or 0.50 mg selenium/kg/day)</td>
<td>2+ years</td>
<td>
<table>
<tr><th>Se (ppm) diet</th><th>Liver tumor incidence (at 18+ months)</th><th>Survival ‹ 18 months)</th></tr>
<tr><td>controls</td><td>‹ 1% hepatic tumors (1/200 living 18 to 24 months, 3/350 living › 24 months [3])</td><td>4/18</td></tr>
<tr><td>5 corn</td><td>2/10 adenomas</td><td>8/18</td></tr>
<tr><td>5 wheat</td><td>2/14 adenomas</td><td>4/18</td></tr>
<tr><td>7 corn</td><td>1 adenoma, 1 carcinoma /10</td><td>8/18</td></tr>
<tr><td>7 wheat</td><td>1 adenoma, 2 adenomatoid hyperplasia/4</td><td>14/18</td></tr>
<tr><td>10 corn</td><td>1 adenoma & low grad carcinoma, 1 low grade carcinoma & adenomatoid hyperplasia, 1 adenomatoid hyperplasia /5</td><td>13/18</td></tr>
<tr><td>10 wheat</td><td>-/3</td><td>15/18</td></tr>
<tr><td>10 selenide</td><td>2 carcinoma low grade, 1 adenomatoid hyperplasia /7</td><td>11/18</td></tr>
</table>
</td>
<td>
Cirrhosis incidence ↑ after 3 months; High mortality in all treatment groups (58%) by end of first 17 ½ months; ↑ Se dose-related.
First tumors after 18 months of treatment; tumors (adenomas-low grade carcinomas) developed only in animals with cirrhotic livers, but authors noted that there was no correlation between degree of cirrhosis and tumor presence: 11 animals with tumors out of 43 animals with cirrhosis of 53 surviving 18+ months, 4(5) with advanced adenomatoid hyperplasia
<table>
<tr><th colspan="4">Liver Tumors</th></tr>
<tr><th colspan="2">Se in diet (ppm)</th><th colspan="2">Se dose (approximate, mg/kg/day)</th></tr>
<tr><th>NOAEL</th><th>LOAEL</th><th>NOAEL</th><th>LOAEL</th></tr>
<tr><td>Control diet</td><td>5</td><td>Control diet</td><td>0.25</td></tr>
</table>
No statistical analysis provided. Authors noted that not all tumors were sectioned, livers with ademonas may have contained carcinomas also and vice versa; and differentiation between adenomas and low grade carcinomas was difficult.

Hoegberg and Alexander 2007 noted possibility that identified tumors actually were regeneration nodules.

ATSDR 2003 noted “The possible contribution of overt hepatotoxicity to the development of liver tumors is not known.”
</td>
</tr>
</table>

[3] As noted in *Harr* et al.

Table 7a (continued)

<table>
<tr><th>Reference</th><th>Test System</th><th>Substance</th><th>Exposure</th><th>Duration</th><th>Tumor Incidence/Cancer-Related Results</th><th>Remarks/Conclusion</th></tr>
<tr><td>Nelson et al. [74], Fitzhugh et al. [207], as cited in [2] (continued)</td><td></td><td></td><td></td><td></td><td>
<table>
<tr><th>Se (mg/kg)</th><th>Animals with adenoma and/ or low-grade carcinoma (at 18+ months)</th><th>Survival ‹ 18 months</th></tr>
<tr><td>controls</td><td>‹ 1%</td><td>22%</td></tr>
<tr><td>5-ppm groups</td><td>4/24 (17%)</td><td>33%</td></tr>
<tr><td>7-ppm groups</td><td>3/14 (21%)</td><td>61%</td></tr>
<tr><td>10-ppm groups</td><td>4/15 (27%)</td><td>72%</td></tr>
</table>
</td><td></td></tr>
</table>

NI: No information
Approximate doses were calculated based on the following conversion: 1 ppm in diet corresponds to 0.150 mg/kg body weight/day for mice, 0.1 mg/kg body weight/day for young rats, 0.05 mg/kg body weight/day for older rats

Table 7b:
Select studies in animal models of cancer and initiation-promotion experiments

<table>
<tr><th>Reference</th><th>Test System</th><th>Substance</th><th>Exposure</th><th>Duration</th><th>Tumor Incidence/Cancer-Related Results</th><th>Remarks/Conclusion</th></tr>
<tr><td>Chen et al. [82] [4]</td><td>M Sprague Dawley Rats oesophageal adeno-carcino-ma (EAC) model (surgical anastomosis + iron supplementation (Fe dextran))</td><td>Sodium selenate (Na_2SeO_4)</td><td>Diet
0.17, 1.7 ppm (~0.13 mg/kg body weight/d)
Control AIN93M diet contained 0.17 mg Se per kg (~0.013 mg/kg bw/d) + 75 IU Vitamin E per kg</td><td>2 weeks be-fore surgery + 40 weeks after</td><td>
<table>
<tr><th>Treatment groups</th><th>EAC incidence</th></tr>
<tr><td>V-Controls</td><td>0 %</td></tr>
<tr><td>I - Controls operated (0.17 ppm Na_2SeO_4)</td><td>67.9 %</td></tr>
<tr><td>II (0.17 ppm Na_2SeO_4) + Vit E 10x</td><td>64.5 %</td></tr>
<tr><td>III
+ 1.7 ppm Na_2SeO_4</td><td>90.3 %</td></tr>
<tr><td>IV
+ 1.7 ppm Na_2SeO_4
+ Vit E 10x</td><td>75 %</td></tr>
</table>
</td><td>Tumor incidence & volume ↑ with dietary Se of 10x standard Se content in diet
This study was dismissed by ATSDR [2] because other studies have shown Se's cancer-protective effects; MAK [8] noted that it could not be used due to its unusual study design
<table>
<tr><th colspan="2">Se in diet (ppm)</th><th colspan="2">Se dose (appro-ximate, mg/kg/ day)</th></tr>
<tr><th>NOAEL</th><th>LOAEL</th><th>NOAEL</th><th>LOAEL</th></tr>
<tr><td>0.17</td><td>1.70</td><td>0.013</td><td>0.13</td></tr>
</table>
</td></tr>
</table>

[4] A later study by the same authors investigated the impact of a low Se/Vitamin E diet versus the regular AIN-93M diet formula (which is supplemented with 0.15 mg Se/kg diet) on N-nitrosomethyl-benzylamine-induced oesophageal squamous cell carcinoma. A continuous low Se/Vitamin E diet resulted in 100% tumor incidence, while supplementation reduced the incidence significantly (up to 28%) (*Yang* et al. 2011). The results of their previous study were not discussed.

Table 7b (continued)

<table>
<tr><th>Reference</th><th>Test System</th><th>Substance</th><th>Exposure</th><th>Duration</th><th>Tumor Incidence/Cancer-Related Results</th><th>Remarks/Conclusion</th></tr>
<tr>
<td>Reddy et al. [85]</td>
<td>M F344 rats
Initiation study
Azoxy-methane s.c. 1x/week for 2 weeks
Initiation (I) group: 1 week after initiation change to control diet
Post-initiation (PI) group: 1 week after initiation change to treatment diet until end of study

27 animals/group</td>
<td>Sodium selenite</td>
<td>Diet
0.1, +0.5, 2.5 ppm
AIN-76A diet with some modifications</td>
<td>Initiation group: 6 weeks (3 weeks before initiation to 3 weeks after)
Post-initiation group: 34 weeks
Controls: 0.1 mg/kg throughout experiment</td>
<td>
<table>
<tr><th>Se (mg/kg diet)</th><th>Total colon tumor (adenoma + adeno-carcinoma incidence (% animals with tumor)</th><th>Total colon tumor multiplicity (number of tumors/animal)</th></tr>
<tr><td>Controls 0.1</td><td>78</td><td>1.62</td></tr>
<tr><td>I: 0.5</td><td>74</td><td>1.56</td></tr>
<tr><td>I: 2.5</td><td>74</td><td>1.04 *); **)</td></tr>
<tr><td>PI: 0.5</td><td>85</td><td>1.73</td></tr>
<tr><td>PI: 2.5</td><td>44 #)</td><td>0.63 #)</td></tr>
</table>
*): significant due to colon adenoma only
**): significant different from the control diet
#): significantly different from the control diet and 0,5-ppm diet

<table>
<tr><th>Se (mg/kg diet)</th><th>Total small intestinal tumor (adenoma + adeno-carcinoma incidence (% animals with tumor))</th><th>Total small intestinal tumor multiplicity (number of tumors/animal)</th></tr>
<tr><td>Controls 0.1</td><td>33</td><td>0.52</td></tr>
<tr><td>I: 0.5</td><td>33</td><td>0.33</td></tr>
<tr><td>I: 2.5</td><td>63 *)</td><td>0.85</td></tr>
<tr><td>PI: 0.5</td><td>37</td><td>0.44</td></tr>
<tr><td>PI: 2.5</td><td>44</td><td>0.59</td></tr>
</table>
GPx activity ↑ in kidney, colon, small intestine of 2.5 ppm Se group
*): significantly different from the control diet and 0,5-ppm diet
</td>
<td>2.5 ppm Se administration during the initiation phase had no effect on total colon tumor incidence, but total small intestinal tumor incidence was ↑ compared to controls and lower dose

2.5 ppm Se administration during the initiation phase had no effect on total colon tumor incidence, but total small intestinal tumor incidence was ↑ compared to controls and lower dose

The authors noted that the protective effect might be due to GPx during post-initiation.
They also hypothesized that an increase in GPx activity of colonic and small intestinal mucosae in Se- supplemented animals may be related to active proliferation of mucosal epithelial cells.</td>
</tr>
</table>

Table 7b (continued)

Reference	Test System	Substance	Exposure	Duration	Tumor Incidence/Cancer-Related Results	Remarks/Conclusion
Perchelet et al. [84]	F CF-1 Mice tumor promotion study to induce skin papilloma via topical application initiaton – 0.1 µmol DMBA (complete carcinogen), + 2 weeks later: 1 stage model: TPA (complete tumor promotor) 2x/week 2 stage model: Stage 1 – TPA 4x, Stage 2 – 2x/week mezerein	Sodium selenite	i.p. injection 40 µg Na_2SeO_3 (~1.6 mg/kg/d) in NaCl/HEPES solution injected 20 min before promoter application Vitamin E was applied 15 min before promoter application	20 weeks 2x/week before each application of promoter treatment (total study duration 22 weeks) Or 1x	1-stage model (ending at 22 weeks): 2 weeks after initiation: TPA + Na_2SeO_3 (20 weeks) Slightly ↓ % survival, % mice with papillomas, and papillomas/mouse ↓ compared to TPA alone. Further ↓ with addition of GSH and/or Vitamin E (with Vitamin E › GSH) 2-stage model (ending at 22 weeks): 2 weeks after initiation Stage 1: TPA + Na_2SeO_3 + Vitamin E (2 weeks); Stage 2: mezerein (20 weeks) slightly ↑ papillomas/mouse 2 weeks after initiation Stage 1: TPA (2 weeks); Stage 2: mezerein + Na_2SeO_3 + Vitamin E (20 weeks Slightly ↑ % survival, ↓mice with papillomas, and ↓ papillomas/mouse compared to TPA/mezerein alone Complete carcinogenesis (ending at 20 weeks): 1x large dose of DMBA + Na_2SeO_3 + Vitamin E Slightly ↓ % mice with carcinomas 2x/week sub-carcinogenic dose of DMBA + Na_2SeO_3 + Vitamin E ↑ number of papillomas/mouse, ↑ % of grade 1 or 4, and ↑ % of mice with carcinomas Enzyme activities: TPA topical + Na_2SeO_3 i.p:. ↑ GPx activity at 5 hrs back to 99% of control (vs 74% with TPA only); ↓ ornithine decarboxylase (ODC) activity at 5 hrs to 78% (vs 100% with TPA) TPA topical + Na_2SeO_3 i.p. + GSH and/or Vitamin E: further ↑ GPx & ↓ ODC (with Vitamin E › GSH) Similar results when mezerein instead of TPA was used	Increase in papilloma per mouse when Se/Vitamin E was injected with TPA during stage 1, but reduction in tumor incidence was observed when injected during stage 2 with mezerein treatment Na_2SeO_3 + Vitamin E ↑ stage 1-promoting activity of TPA Na_2SeO_3 + Vitamin E ↑ tumor incidence with chronic low-dose DMBA Limitation: Sodium selenite only studied together with Vitamin E The authors suggested that *"under certain experimental conditions, different doses of Na_2SeO_3 can either decrease or enhance the carcinogenic process, possibly through modulations of the GSSG-GSH ratio and inhibition of cell proliferation (54). If, for instance, adaptive cell proliferation occurs in response to high Na_2SeO_3 in an organ, an enhancement of carcinogenesis is likely, resulting in the development of cells that are resistant to high doses of Na_2SeO_3 (54)"* [54: *LeBoeuf* et al. [83]

Table 7b (continued)

Reference	Test System	Substance	Exposure	Duration	Tumor Incidence/Cancer-Related Results	Remarks/Conclusion
LeBoeuf et al. [83]	F SD rats 1) Partial hepatectomy + DEN[5] Control diet for 1 week, then Se diet for 16 weeks 2) Partial hepatectomy + DEN Control diet for 1 week, then 6 ppm Se diet for 9 weeks, then control diet + pheno-barbital M Fischer 344 rats 3) 4x 4-week cycles of AAF + 6 ppm Se interrupted by 1-week control diet 4) 4 cycles of AAF for 20 weeks + control diet, then 21 weeks of Se-diet 0, 3, 6 ppm	Sodium selenite As Selenium: glucose mono-hydrate	Diet 0.1, 3.0, 6.0 ppm	1) 16 weeks -after initia-tion 2) 9 weeks -after initiation but before promotion with PB 3) 4x 4 weeks 4) 21 weeks	1) 3 & 6 ppm Se ↓ focal growth rate, but not number of GGT foci (temporary & reversible with 6 ppm Se – selenosis?) 2) 6 ppm Se ↑ slightly number of foci/ liver area & mean focal volume, ↑ GGT focal volume/liver volume 3) 6 ppm Se ↓ mean focal volume & focal volume/liver volume, but no effect on number of foci/liver area 4) 3 ppm Se no effect; 6 ppm no effect on hepatocellular incidence (100%) but ↓ liver lesion volume/total liver volume	Se increased tumor-promoting potency of phenobarbital; Effect on focal growth but not number of lesions – can be ↓ or ↑ depending on when given in rela-tionship to promotor The authors concluded that the *"effects of selenium on focal growth may represent a 'selective toxicity' to proliferating cells compared to a relatively nonproliferating background and thereby decrease carcinogenesis"*. They further concluded *"if however adaptive cell proliferation occurs in response to high selenium in an organ, an enhancement of carcinogenesis is likely, resulting in development of cells that are resistant to high doses of seleni-um. A selenium interaction with tumor promoters may also enhance promoting activity. "* The authors also suggested that *"continued administration of seleni-um is necessary for the anticarcino-genic effects"* because there was no removal or repair of preneoplastic lesions under selenium treatment.

[5] DEN: Diethylnitrosamine

Table 7b (continued)

<table>
<tr><th>Reference</th><th>Test System</th><th>Substance</th><th>Exposure</th><th>Duration</th><th>Tumor Incidence/Cancer-Related Results</th><th>Remarks/Conclusion</th></tr>
<tr>
<td>Shamberger [209]; Shamberger and Frost [49]</td>
<td>Mice F albino ICR Swiss

Dietary experiments:
36 mice/group

3) Tumor promotion study: 1x application of 7,12-dimethylbenz[a]-anthracene (DMBA) in acetone to the skin + after 3 weeks 0.05% croton oil in acetone daily for 20 weeks; DMBA only

4) Complete carcinogen study: daily applications of 0.03% solution of B[a]P in acetone for 27 weeks</td>
<td>Sodium selenite, sodium selenide

Na_2SeO_3
MW = 172.93774 g/mol,
Na_2Se
124.93954 g/mol,
Se
78.96 g/mol</td>
<td>Diet
Tortula yeast diets containing added
0, 0.1, 1.0 mg/kg selenium selenite (= 0.13 mg Se/kg body weight/day),
0.1 mg/kg sodium selenide
Corresponding to
0, 0.046, 0.46 mg/kg Se as Na_2SeO_3
0.063 mg/kg Se as Na_2Se</td>
<td>Starting 2 weeks before initiation until study end</td>
<td>Tumor-Promotion Experiment:
1x DMBA + 3 weeks later – daily application of croton oil for 20 weeks + different diets (starting 2 weeks before initiation)

Authors describe that 14/35 (40%) of mice on 1-ppm diet versus 26/36 (72%) of mice on Se-deficient diets had developed papillomas at 20 weeks (P<0.01)

Based on Figure 1:
<table>
<tr><th>Diet</th><th>% of mice with tumors/ papilloma</th></tr>
<tr><td>Rockland diet</td><td>~87%</td></tr>
<tr><td>0.046 ppm Se as Na_2SeO_3</td><td>~80%</td></tr>
<tr><td>Torula controls</td><td>~72%</td></tr>
<tr><td>0.063ppm Se as Na_2Se</td><td>~57%</td></tr>
<tr><td>› 0.46 ppm Se as Na_2SeO_3</td><td>~40%</td></tr>
</table>
Complete carcinogenesis:
Instead of DMBA, the complete carcinogen B[a]P was applied daily for 27 weeks
<table>
<tr><td colspan="4">Daily skin application of B[a]P</td></tr>
<tr><td>ppm Se added</td><td>Mice with tumors at 22 weeks</td><td>Mice with cancer at 27 weeks</td><td>Lesions/ mouse at 27 weeks</td></tr>
<tr><td colspan="4">Rockland diet</td></tr>
<tr><td>0</td><td>34/36 (94%)</td><td>16/35 (46%)</td><td>11.5</td></tr>
<tr><td colspan="4">Torula yeast</td></tr>
<tr><td>0</td><td>31/36 (86%)</td><td>16/35 (40%)</td><td>8.1</td></tr>
<tr><td>0.046</td><td>26/36 (72%)</td><td>22/36 (61%)</td><td>9.8</td></tr>
<tr><td>0.063</td><td>18/35 (51%)</td><td>12/35 (29%)</td><td>6.8</td></tr>
<tr><td>0.46</td><td>16/36 (44%)</td><td>8/33 (24%)</td><td>5</td></tr>
</table>
</td>
<td>No info on background Se levels in Torula yeast provided
Dietary Se levels influenced tumor development in models:
Lowest tumor incidences for highest Se dose added compared to Se-deficient diets, and less lesions per mouse.</td>
</tr>
</table>

Table 8:
In vitro genotoxicity of selenium and its inorganic compounds

Endpoint	Reference	Test System	Test Substance	Dose range (No. of Dose Groups)	Effective Concentration	Cytotoxic Concentration	Results	
							-S9	+S9
Bacteria								
DNA Damage	*Yasunaga* et al. [210]	*S. typhimurium* TA1535/pSK1002	Na_2SeO_3	0 to 600 µM	NA	600 µM	+	.
	Cemeli et al. [211]	*S. typhimurium* TA102	Na_2SeO_4	3.5 to 70 µM (6)			-	nd
		S. typhimurium TA102	Na_2SeO_3	4 to 80 µM (6)			-	nd
		S. typhimurium TA102	H_2SeO_3	4.6 to 92 µM (6)			-	nd
	Noda et al. [105]	*B. subtilis*	Na_2SeO_3	50 µM		NA	+	
	Nakamuro et al. [212]	*B. subtilis*	Na_2SeO_3	1 to 10 mg/ml (2)		NA	+	
Yeast								
Gene mutation	*Letavayova* et al. [213]	*S. cerevisiae* SRJ751	Na_2SeO_3	100 to 10,000 µM (5)	100 µM	100 µM	+	nd
			Se-Met	100 to 10,000 µM (5)			-	nd
Mammalian cells								
DNA damage	*Snyder* et al. [214]	Human fibroblasts	Na_2SeO_3	25 to 500 µM (4)	≥50 µM: glutathione increased effect	NA	+	
Strand breaks	*Lu* et al. [215]	Mouse leukemia cells	Na_2SeO_3	5 to 20 µM (3)	≥5 µM, ss breaks; ≥10 µM, ds breaks	NA	+	
	Wilson et al. [216]	Mouse leukemia cells	Na_2SeO_3	20 µM		NA	+	
	Lo et al. [217]	Human fibroblasts	Na_2SeO_3	0.08 to 3.0 mM (6)		NA	+	+
	Garberg et al. [218]	Hepatocytes	Na_2SeO_3	20 to 40 µM (4)	≥30 µM, only when O_2 was added	50 µM	+	
DNA repair	*Lo* et al. [217]	Human fibroblasts	Na_2SeO_3	0.08 to 3.0 mM (6)	≥0.8 mM –S9 (max 20x); ≥0.3 mM +S9	1.0 mM	+	+
	Whiting et al. [219]	Human fibroblasts	Na_2SeO_3	0.1 µM to 10mM (10)	≥100 µM; glutathione increased effect	1.0 mM	+	
	Russell et al. [220]	Hepatocytes	Na_2SeO_3	100 µM		NA	+	
DNA-Damage, Comet-Assay	*Cemeli* et al. [211]	Human lymphocytes	Na_2SeO_4	100 to 1,000 mM (4)	≥100 mM		+	nd
			Na_2SeO_3	100 to 1,000 mM (4)	≥100 mM		+	nd
			H_2SeO_3	3 to 15 mM (5)	≥3 mM		+	nd
		TK6-Cells	Na_2SeO_3	1 or 10 µM			–	nd

Table 8:
In vitro genotoxicity of selenium and its inorganic compounds

Endpoint	Reference	Test System	Test Substance	Dose range (No. of Dose Groups)	Effective Concentration	Cytotoxic Concentration	Results	
							-S9	+S9
SCE	*Sirianni* and *Huang* [221]	V79 Cells	Na_2SeO_3	1.4 to 185 µM (8)	185 µM -S9; ≥11.5µM + S9		+	+
	Ray and *Altenburg* [223]	Human lymphocytes (whole blood or erythrocyte lysate)	Na_2SeO_3	1.5 to 15.8 µM (4)	≥7.9 µM	NA		+
	Ray and *Altenburg* [223]	Human lymphocytes in whole blood	Na_2SeO_3	1.19 to 39.5 µM (7)	≥11.9 µM	NA		+
	Ray [224]		Na_2SeO_3	7.9 to 11.9 µM (2)	≥ 7.9 µM	NA		+
	Ray and *Altenburg* [222]	Human lymphocytes, purified	Na_2SeO_3	1.6 to 79 µM (5)		79 µM lethal	–	nd
		Human lymphocytes in whole blood	Na_2SeO_3	1.6 to 79 µM (5)	≥7.9 µM	≥15.8 µM	+	nd
			Na_2Se	1.12 to 40.0 µM (7)	≥11.2 µM	NA	+	nd
			SeO_2	1.12 to 40.0 µM (7)	≥11.2 µM	NA	+	nd
			Se	1.6 to 40.0 µM (8)	≥8.0 µM	NA	+	nd
			Na_2SeO_4	1.12 to 79.9 µM (8)		NA	–	nd
Chromosome Aberrations	*Newton* and *Lilly* [119]	Rat lymphocytes	Na_2SeO_3	1 to 25 µM (5)	≥7.5 µM	NA		+
	Nakamuro et al. [212]	Human lymphocytes	Na_2SeO_3	1.3 to 2.6 µM (2)		NA		+
	Khalil [225]	Human lymphocytes	Na_2SeO_3	0.08 to 800 µM (4)	≥0.08 µM	NA		+
	Lo et al. [217]	Human fibroblasts	Na_2SeO_3	0.02 to 3.0 mM (9)	≥80 µM -S9; ≥20 µM +S9	≥0.8 mM	+	+
	Whiting et al. [219]	CHO cells	Na_2SeO_3	0 to 500 µM (7)	≥100 µM	500 µM0		+
	Biswas et al. [226]	Human lymphocytes	Na_2SeO_3	0.2 to 29 µM (5)	≥0.2 µM	≥2.9 µM; lethal at 29 µM	+	nd
			Na_2SeO_4	1.1 to 26.5 µM	≥1.1 µM	≥10.1 µM; lethal at 26.5 µM	+	nd
	Bronzetti et al. [227]	V79-Cells	Na_2SeO_3	0.5 µM	–	0.7 µM (determined in pretest)	–	nd

Table 8:
In vitro genotoxicity of selenium and its inorganic compounds

Endpoint	Reference	Test System	Test Substance	Dose range (No. of Dose Groups)	Effective Concentration	Cytotoxic Concentration	Results	
							-S9	+S9
Micronuclei	*Berces* et al. [228]	Human lymphocytes	Na_2SeO_3	0.1 to 100 µM (4)	≥10 µM increased slightly	≥100 µM		
	Cemeli et al. [229]	Human lymphocytes in whole blood	Na_2SeO_3	0.1 or 1 µM	–	≥0.10 µM	–	nd
			Na_2SeO_4	5 or 50 µM	–	50 µM	–	nd
			H_2SeO_3	0.5 or 5 µM	–	≥0.5 µM	–	nd
		TK6-Cells	Na_2SeO_3	1 or 10 µM	1 µM	≥1 µM	+	nd
			Na_2SeO_4	10 or 100 µM	100 µM	100 µM	+	nd
			H_2SeO_3	1 or 10 µM	1 µM	≥1 µM	+	nd
Gene mutation TK+/– Test	National Toxicology Program [113]	Mouse lymphoma cells	SeS	–S9: 1.13 to 18 µM (6) +S9: 4.5 to 54 µM (6)	–S9: 1.13 µM	–S9: 6.75 µM +S9: not toxic	+	–