Level 2 - Details on Dioxins

1. **What are dioxins?**
   1.1 What are dioxins chemically?
   1.2 How are dioxins formed?
   1.3 What happens to dioxins when they enter the environment?

2. **How are humans exposed to dioxins?**
   2.1 What are the principal source of exposure to dioxins?
   2.2 What are the other possible sources of dioxin contamination?
   2.3 How do dioxins act on living organisms?

3. **What are the effects of dioxins in laboratory animals?**
   3.1 What are the non-cancer effects on animals?
   3.2 Do dioxins cause cancer in laboratory animals?

4. **What are the effects of dioxins on human health?**
   4.1 Have dioxins caused cancer to humans?
   4.2 What non-cancer effects have been observed in children?
   4.3 What non-cancer effects have been observed in adults?

5. **How can dioxin exposure be linked to health effects?**
   5.1 Is there a known relationship between dioxin exposure and cancer?
   5.2 Can a model predict non-cancer effects?
   5.3 How are dioxins mixtures accounted for?

6. **Evaluation and conclusions**
   6.1 Human exposure to Dioxins
   6.2 Observed health effects
   6.3 Tolerable Daily Intake set by WHO for dioxins
   6.4 Breastfeeding

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This Digest is a faithful summary of the leading scientific consensus report produced in 1998 by the International Programme on Chemical Safety (IPCS) of the World Health Organization (WHO):

"Executive Summary of the Assessment of the health risk of dioxins"

The full Digest is available at: https://www.greenfacts.org/en/dioxins/
1. What are dioxins?

1.1 What are dioxins chemically?

The term "dioxins", commonly covering polychlorinated dibenzo-dioxins (PCDDs) and polychlorinated dibenzo-furans (PCDFs), refers to a group of chlorinated organic chemicals with similar chemical structures.

Chlorine atoms can be attached to 8 different places on the molecule, numbered from 1 to 8. Dioxins can have varying harmful health effects depending on the number and position of the chlorine atoms. 2,3,7,8-TCDD or simply TCDD, a molecule with 4 chlorine atoms, is one of the two most toxic dioxins. Only dioxins having more chlorine atoms added to the 2,3,7,8-TCDD structure are also toxic, but to a lesser extent. Other dioxins do not show this dioxin-type toxicity.

Chlorinated chemicals with comparable structural and biochemical properties, such as certain polychlorinated biphenyls (PCB), are called "dioxin-like compounds" and can act similarly in terms of dioxin-type toxicity.

Dioxins are almost insoluble in water but have a very high affinity for lipids (fat). They also tend to associate with organic matter such as ash, soil and plant leaves.

1.2 How are dioxins formed?

Dioxins mainly derive from human activities, but can to a lower extent also be generated naturally by forest fires or volcanic activity.

Dioxins have no use as such and are formed unintentionally by industrial processes and incomplete combustion, for instance: municipal and domestic waste incineration, burning fuels (wood, coal or oil), chlorine bleaching of pulp and paper and chlorinated pesticides manufacturing.

Burning of many materials containing chlorine, such as plastics, wood treated with pentachlorophenol (PCP), pesticide-treated wastes, other polychlorinated chemicals (PCBs), and even bleached paper can produce dioxins. Cigarette smoke, home-heating systems, and exhaust from cars also contain small amounts of dioxins.

PCBs have been widely used as a dielectric and cooling fluid for electrical equipment such as transformers.

1.3 What happens to dioxins when they enter the environment?

After emission in the atmosphere, dioxins are deposited on land or water, close to or far from the emission sources depending on the size of the particles they associate with.
Dioxins in water bind strongly to small particles, organic matter or plankton. Dioxins deposited on land bind strongly to the soil and therefore most often do not contaminate groundwater.

Most of the dioxins found in plants come from air and dust or from dioxin-containing pesticides or herbicides. Plants and animals are eaten by larger animals, which accumulate dioxins in their body and milk (bioaccumulation). Because dioxins bind to fat and are very stable, their concentrations increase with each step in the food chain (biomagnification).

2. How are humans exposed to dioxins?

Three ways of exposure to dioxins exist: background exposure (mainly through diet), industrial accidents and workplace contamination.

2.1 What are the principal source of exposure to dioxins?

2.1.1 Over 90 percent of human background exposure to dioxins occurs through the diet, essentially with fats from animal origin. Dioxins emitted by various sources deposit on farmland and water bodies and bioaccumulate in the food chains. Other sources of food contamination include contaminated animal feed, sewage sludge contaminated with dioxins, flooding of pastures, waste effluents and inappropriate food processing.

2.1.2 In industrialized countries, the daily intake of dioxins [see Annex 1, p. 10] (PCDDs and PCDFs) is in the order of 1-3 pg I-TEQ per kg body weight per day [see Annex 1, p. 10], which is close to the Tolerable Intake value set by the World Health Organization (WHO) (see question 6.3). If PCBs are included, the daily intake can be 2 or 3 times higher. Diets low in animal fat result in lower intakes, while consumption of highly contaminated foodstuffs may lead to higher intakes. The body burden of dioxins increases during childhood and reaches an equilibrium around the age of 20.

2.1.3 During growth, the intake per kilogram of body weight decreases partly as a result of an increasing average body weight. Recent studies from the Netherlands, United Kingdom and Germany show decreasing dioxin levels in food and consequently a dietary intake lower by almost 2 since the early 90's.

2.1.4 For breast fed babies, the daily intake of dioxins [see Annex 1, p. 10] per kg of body weight may be ten to hundred times greater than for adults. Breast milk is more contaminated in industrialized areas (10-35 pg I-TEQ [see Annex 3, p. 11] /g milk fat) than in developing countries (< 10 pg I-TEQ [see Annex 3, p. 11] /g milk fat). However, the levels are decreasing, especially in industrialized countries. Individual contamination can vary by a factor of 5 to 10, depending on age of the mother, number of breastfed babies, length of nursing period and food habits.

2.2 What are the other possible sources of dioxin contamination?

2.2.1 Local populations can be accidentally exposed to high dioxin levels, like in Seveso (Italy) in 1976, after an explosion at a chemical factory, or from fires in electrical equipment containing PCBs. Accidental contamination of rice oil in Japan and Taiwan resulted in intakes of dioxin-like compounds many thousand times higher than normal.

2.2.2 Industrial activities in which dioxins are unintentionally produced (such as waste incineration or production of certain pesticides or chemicals) may result in exposures of
certain workers. In the past, some workers accidentally exposed to high concentrations of dioxins had TCDD blood levels up to thousands of times higher than usual, but today, many industrial sources of dioxins have been identified and the workers' overall exposure has been reduced or eliminated.

2.3 How do dioxins act on living organisms?

2.3.1 The toxic dioxins can alter key biochemical and cellular functions by interacting with a cellular receptor called Ah, affecting the hormonal system and the way cells grow and develop. The mechanism of action of dioxins appears to be the same in both humans and animals.

2.3.2 Being highly lipophilic, dioxins dissolve in fat. They need to be transformed in the liver to become water soluble before they can be excreted. However, dioxins are metabolized slowly and therefore tend to bioaccumulate, especially in fat and in the liver.

The speed of elimination of dioxins can vary with dose, quantity of body fat, age and sex. The process of elimination of dioxins and PCBs is similar in animals and man, but it is faster in most other mammals. Rodents only reach the same body burdens, or tissue concentration, at much higher exposure compared to humans. This is why body burden must be used as a reference when comparing risks for humans and animals.

The biological half-life, which technically characterizes the speed of elimination, varies largely for the various dioxins and dioxin-like compounds. However the average half-life of 2,3,7,8-TCDD is being used for practical purposes.

3. What are the effects of dioxins in laboratory animals?

3.1 What are the non-cancer effects on animals?

Toxic dioxins, especially 2,3,7,8-TCDD, can cause multiple non-cancer effects in animals at varying doses. Direct effects can be toxic or not. Non-toxic effects observed at low dose may or may not result subsequently in toxic effects in the animal or its offspring.

Some of the toxic effects observed at lower exposures are endometriosis (uterine disease), neurobehavioral (cognitive) effects, reduced sperm counts, female urogenital malformations and effects on the immune system.

Dioxin levels in the general population of industrialized countries sometimes reach the lower levels at which significant effects have been observed in animals.

3.2 Do dioxins cause cancer in laboratory animals?

2,3,7,8-TCDD has been shown to be carcinogenic to multiple animal species of both sexes. Most dioxins do not initiate cancer as such, but indirectly promote growth and proliferation of previously initiated cancerous lesions.

The cancer observed at the lowest exposure are liver tumors in rats. 2,3,7,8-TCDD also caused thyroid tumors in male rats.
Several other dioxin types have also been shown to be cancer promoters.

4. What are the effects of dioxins on human health?

4.1 Have dioxins caused cancer to humans?

4.1.1 Most information on the carcinogenicity of the dioxin 2,3,7,8-TCDD in humans comes from epidemiological studies of both accidentally exposed workers in herbicide plants and people living near the Seveso chemical factory in Italy.

However, most studies concern mixtures of several kinds of dioxins. As such, the evaluation of risks for individual dioxins is difficult. The 2,3,7,8-TCDD levels of exposed herbicide workers were comparable to the ones that induced liver cancers in rats, but on average, the exposures around Seveso were lower.

4.1.2 Herbicide plant workers heavily exposed to dioxins had more cancers of all types combined than the general population. The number of cancers increased with exposure (dose-response relationship).

In Seveso, the number of deaths due to cancer has not increased since the accident, but it is still too early to reach definite conclusions. However, several studies showed excess risks for some specific cancers.

A 22 year study of people in Japan who ate rice oil highly contaminated with PCBs and other dioxin-like compounds, showed an increase in liver cancer. No cancer increase was found after 12 years for another group in Taiwan who ate rice oil that was less contaminated.

In summary, there is strong evidence that people accidentally exposed to the highest dioxin levels had an increased overall cancer risk (about 40% increase); there is less strong evidence of increased risks for specific cancers. In comparison, the average exposure of the general population is a hundred to a thousand times lower for TCDD and ten to hundred times lower for all dioxins combined.

4.2 What non-cancer effects have been observed in children?

Studies showed neurodevelopmental delays and neurobehavioral effects in children. The effects are attributed to exposure of the unborn child through the placenta rather than through breast feeding. These effects even occurred at background levels, but only affected the infants with the highest exposure. In at least one US study, mothers were, however, simultaneously exposed to chlorinated pesticides and heavy metals.

Following the rice oil contamination incidents in Japan and Taiwan, effects, at least partly related to dioxins, were observed in new born children due to pre-birth exposure. Effects included skin defects, general persistent development delays, low birth-weight, mild behavioral disorders, decrease in penis length at puberty, reduced height among girls at puberty and hearing loss.

A study in the Netherlands showed that breast fed infants had a better neurobehavioural development compared to formula fed infants. However, within the group of breast fed infants, those receiving milk with higher dioxin content had poorer neurobehavioural test results.
In Seveso, it was observed that fathers highly exposed to TCDD had a lower boy to girl birth ratio than normal.

### 4.3 What non-cancer effects have been observed in adults?

Information on effects in adults comes from several studies of populations exposed to high levels of dioxins: the US Air Force staff who were exposed to the Agent Orange defoliant in Vietnam, a second study in Vietnam, studies in the populations around the Seveso chemical factory, and of the contaminated rice oil incidents in Japan and Taiwan.

Exposed workers showed biochemical effects including elevated levels of gamma GT, triglyceride and glucose in blood and an increase in diabetes. In Seveso, data show an increased death rate in women from diabetes and from cardiovascular diseases in men. A higher rate of heart diseases was also observed in some occupationally exposed groups of men.

Adults affected by contaminated rice oil experienced various effects including a skin rash called chloracne, conjunctivitis, sebaceous cysts and inflammation, decreased nerve conduction velocity, fatigue and malaise, skin problems (hyperpigmentation and hyperkeratosis), as well as an increased death rate from non-cancer liver diseases.

### 5. How can dioxin exposure be linked to health effects?

#### 5.1 Is there a known relationship between dioxin exposure and cancer?

5.1.1 Lifetime dose-effect relationships for cancer were derived from workers moderately exposed to dioxins. The results suggest that a continuous exposure at work to between 2 and 7 pg TCDD per kg body weight per day increases the risk of cancer by 1%. Over a lifetime, this would result in a body burden of 3 000 to 13 000 pg TCDD per kg body weight.

5.1.2 To compare humans and animals, only body burdens are relevant; indeed, rats and mice need to ingest much more dioxins than humans to reach the same body burden.

Two approaches were used to evaluate cancer risks from experimental animal studies and led to very different results. The first one is based on the knowledge of mechanisms that increase cell multiplication, inducing liver tumors in female rats. It concluded that a body burden of 2 600 pg per kg body weight [see Annex 2, p. 10] increases the risks of cancer by 1%.

A second, graphical model used the results of a series of cancer studies on rats and mice; it concluded that a body burden of 10 000 to 746 000 pg per kg body weight increases the risk of cancer by 1%.

#### 5.2 Can a model predict non-cancer effects?

Currently, models cannot adequately predict non-cancer effects in humans, partly because the mechanisms of action are not yet fully understood. However, they may provide additional insights in understanding the effects observed in experiments.
5.3 How are dioxins mixtures accounted for?

5.3.1 Dioxins are generally found in mixtures containing several kinds of dioxins and dioxin-like compounds, each having its own degree of toxicity.

Therefore each is attributed a specific toxic factor called Toxic Equivalency Factor (TEF [see Annex 3, p. 11]). This factor indicates a relative toxicity compared to the most toxic dioxin, 2,3,7,8-TCDD, which is given a reference value of 1 (see table 3). The TEF [see Annex 3, p. 11] scheme refers only to adverse effects (e.g. cancer) following interactions with the cellular Ah-receptors. Other toxic effects of dioxins and dioxin-like compounds cannot be quantified by this method.

The overall toxicity of a dioxin mixture is calculated by:

1. multiplying the individual quantity of each compound by its specific TEF [see Annex 3, p. 11] value and
2. summing the values obtained to get a total TCDD “toxic equivalent” (TEQ [see Annex 3, p. 11]) for the mixture.

TEF [see Annex 3, p. 11] values are attributed on the assumptions that a compound must:

- show a structural relationship to the dioxins (PCDD’s and PCDF’s).
- bind to the dioxin cellular Ah-receptors.
- cause effects via this Ah receptor.
- be persistent and accumulate in the food chain.

5.3.2 In the majority of experimental studies, the effects are additive and the TEQ [see Annex 3, p. 11] calculation works well. However, some non-additive effects of PCDD, PCDF and PCB mixtures have been reported. These may be due to effects of the individual compounds on each other’s metabolism and, for some PCBs, to other mechanisms of action than those occurring via the Ah-receptor.

When used with caution, the TEF [see Annex 3, p. 11] approach is a valuable tool for expressing a daily intake for most dioxins and comparing it to the Tolerable Daily Intake (TDI).

6. Evaluation and conclusions

6.1 Human exposure to Dioxins

6.1.1 In most industrialized countries, concentrations of dioxins in environmental samples, foods, human tissues and breast milk have decreased during the 1990s, mainly due to enforced environmental regulations.

In industrialized countries, the daily intake of dioxins [see Annex 1, p. 10] (PCDDs and PCDFs) is in the order of 1 to 3 pg I-TEQ per kg body weight per day [see Annex 1, p. 10]. If PCBs are included, the daily intake is up to 3 times higher, hereby exceeding the Tolerable Daily Intake (TDI) as put forward by the World Health Organization (WHO) (see 6.3).

Breast milk is less contaminated in developing countries (<10 pg/g milk fat) than in industrialized countries (10-35 pg/g milk fat). For breast-fed infants, the daily intake [see Annex 1, p. 10] per kg of body weight is ten to hundred times greater than for adults, but has been reduced since the early 90’s by up to 50% in most industrialized countries.
Generally 2,3,7,8-TCDD accounts for only 10 to 20 % of the total dioxin TEQ [see Annex 3, p. 11] -exposure and for less than 5% when dioxin-like PCBs are included.

6.1.2 Several factors determine the persistence of dioxins in the body, including dose, quantity of body fat, binding to liver proteins and rate of metabolic transformation and excretion.

Both humans and animals accumulate dioxins. Body burden is the most appropriate parameter to compare exposure and effects between species. Because of differences in the above factors, rodents need to ingest 100 to 200 times more dioxins than humans to reach a same body burden.

Because dioxins remain in the human body for a relatively long time, higher intakes for a short period will not result in significant changes to the long-term body burden.

6.2 Observed health effects

Dioxins can alter key biochemical and cellular functions by binding to the cellular Ah-receptor. The broad range of Ah-receptor binding affinities seen in human placenta samples suggests that the response to dioxins varies significantly from one person to another (see question 2.3).

A number of biochemical effects have been observed in experimental animals at body burdens comparable to those of the general human population. These effects may be harmful or not, and may or may not be due to interactions with the cellular Ah-receptors. To evaluate the risks for human populations, studies usually focus on the effects observed at the lowest doses. Toxic effects were observed on animals at body burdens in the range of 10 000 to 73 000 pg per kg body weight [see Annex 2, p. 10]. A human daily intake can be calculated which would correspond to these animal body burdens.

The following non-cancer effects were observed:

- Mothers that were accidentally exposed to very contaminated rice oil, leading to an extremely high body burden of 2 to 3 million pg TEQ per kg body weight, gave birth to infants showing severe and persistent developmental and neurological effects.
- In workers exposed to high levels of dioxins in their workplace, health effects were observed at body burdens ranging from 28 000 to 400 000 pg per kg body weight [see Annex 2, p. 10]. These effects include changes in the blood composition and increased cardiovascular diseases and diabetes.
- Some of the Seveso population, which was exposed to PCDDs and PCDFs at levels up to ten to hundred times higher than normal, suffered some temporary effects, such as a skin rash called chloracne and blood biochemistry changes. An increase in male cardiovascular deaths and a decrease in the boy to girl birth ratio were observed.

Humans may be as sensitive as animals to the carcinogenic effects of dioxins. Accidental exposure to TCDD at levels hundred to thousand times higher than those of the general population (ten to hundred times higher TEQ [see Annex 3, p. 11] values in terms of total dioxins) increases the risk for all cancers combined by 40%.

Concerning the effects on birth weight, thyroid hormone effects and nervous system development, the interpretation of the results is complicated by simultaneous exposure to other chemicals. Some effects were observed at dioxin levels only slightly higher than the exposure of the general population.
6.3 Tolerable Daily Intake set by WHO for dioxins

6.3.1 The World Health Organization (WHO) recommends a Tolerable Daily Intake (TDI) of 1 to 4 pg WHO-TEQ/kg body weight per day [see Annex 1, p. 10]. This figure is based on the lowest exposures at which adverse effects were observed in experimental animals. It includes an overall uncertainty factor of 10, in order to account for possible differences in susceptibility between humans and experimental animals and in between people.

6.3.2 The TDI represents a tolerable daily intake for a life-time exposure. Occasional exceeding of the TDI should have no health consequences, provided that the averaged intake over longer periods remains below it. In industrialized countries, some people exceed the TDI and may therefore show some subtle effects which have, however, not been proven to be harmful.

The upper limit of 4 pg WHO-TEQ/kg body weight per day [see Annex 1, p. 10] is provisional: the ultimate goal is to reduce human intake levels below 1 pg WHO-TEQ/kg body weight per day [see Annex 1, p. 10]. The World Health Organization (WHO) recommended that every effort should be made to limit emissions of dioxins and related compounds in order to reduce their presence in the food chain. Immediate efforts should specifically target exposure reductions of highly exposed sub-populations.

6.4 Breastfeeding

Breast-fed infants have higher intakes of dioxins but only during a small period of their life. Some studies found subtle effects in children of mothers exposed to dioxins, but these effects are, in all but one study, probably due to exposure through the placenta rather than through breast milk.

Breastfeeding has many beneficial effects. Therefore, the World Health Organization (WHO) promotes breastfeeding while recommending the reduction of dioxin emissions. Dioxin levels in human milk have decreased since the early 90's.
Annex

Annex 1:
Daily Dioxin Intakes

The long-term intake of dioxins can be expressed in:
- picogram I-TEQ [see Annex 3, p. 11] per kilogram of body weight per day (pg I-TEQ/kg body weight per day, pg I-TEQ/kg bw.day)
- picogram I-TEQ [see Annex 3, p. 11] per person per day (pg I-TEQ/person/day); to convert from one unit to the other, it is generally assumed that an adult person weighs 60 kg.

In these units, I-TEQ stands for International Toxicity Equivalent (and is sometimes omitted in writing).More... [see Annex 3, p. 11]

The uptake of dioxins by living organisms leads to accumulation in the body, resulting in a body burden [see Annex 2, p. 10].More... [see Annex 2, p. 10]

Some average daily intakes for long term exposures to dioxins:

<table>
<thead>
<tr>
<th>Daily intake (pg I-TEQ per kg body weight per day)</th>
<th>See question</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rice oil contamination with PCBs in Japan (over 1 month)</td>
<td>2.2.1 [see <a href="https://www.greenfacts.org/en/dioxins/l-3/dioxins-2.htm#ip21">https://www.greenfacts.org/en/dioxins/l-3/dioxins-2.htm#ip21</a>]</td>
</tr>
<tr>
<td>Tolerable Daily Intake, TDI (over a life time)</td>
<td>6.3.1 [see <a href="https://www.greenfacts.org/en/dioxins/l-3/dioxins-99.htm#ip31">https://www.greenfacts.org/en/dioxins/l-3/dioxins-99.htm#ip31</a>]</td>
</tr>
</tbody>
</table>

a This is the estimated human long term intake corresponding to the “Least Observed Adverse Effect Level” for the most sensitive adverse responses reported in experimental animals.

Annex 2:
Dioxin Body Burden

Dioxins taken-in by living organisms (see Daily Dioxin Intakes) [see Annex 1, p. 10] and absorbed into the body (uptake), are able to accumulate in the body, resulting in a body burden, which is the total amount of dioxin uptake present in the body at any one time.

For dioxins, the body burden is usually expressed in:
- Mass (weight) Units I-TEQ [see Annex 3, p. 11] per kilogram of body weight (pg I-TEQ/kg bw)
- Alternatively, as dioxins accumulate in fat, the body burden can be expressed in picogram I-TEQ [see Annex 3, p. 11] per gram of serum lipid, i.e. per gram of fatty substance in the blood (pg I-TEQ/g lipid).

Instead of the weight unit picogram (pg), nanogram (ng) can be used, 1000 pg being 1 ng.

In these units, I-TEQ [see Annex 3, p. 11] stands for International Toxicity Equivalent (and is sometimes omitted in writing).More [see Annex 3, p. 11]
Some Body Burdens at the time of exposure:

<table>
<thead>
<tr>
<th></th>
<th>in pg I-TEQ per kg body weight</th>
<th>in pg I-TEQ per g serum lipid</th>
<th>See question</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults in industrialized countries</td>
<td>2 000 to 6 000</td>
<td>10 to 30 **</td>
<td>2.1.2 &amp; 7.1.1</td>
</tr>
<tr>
<td>Moderately exposed workers</td>
<td>3 000 to 13 000</td>
<td>15 to 650 **</td>
<td>5.1</td>
</tr>
<tr>
<td>Highly exposed workers</td>
<td>26 000 to 400 000</td>
<td>140 to 2 400 **</td>
<td>2.2.2 &amp; 7.2</td>
</tr>
<tr>
<td>SEVESO incident (median values)</td>
<td>Zone A: 90 000 * Zone B: 25 000 * Max : 10 000 000</td>
<td>About 50 **</td>
<td>2.2.1</td>
</tr>
<tr>
<td>US Air Force Ranch hands in Vietnam</td>
<td>About 10 000</td>
<td>About 50 **</td>
<td>4.3</td>
</tr>
</tbody>
</table>

* Derived by dividing the body burden in lipids by a factor of 5.
** Derived by multiplying the body burden per body weight by a factor of 5.

See also "Estimated tissue concentrations in human populations exposed to dioxin and dioxin-like compounds" in Table 2 question 4.3.

**Annex 3:**

**Toxic Equivalents Scheme (TEFs & TEQs)**

Dioxins are generally found in mixtures containing several kinds of dioxins and dioxin-like compounds, each having its own degree of toxicity. To express the overall toxicity of such a mixture as a single number, the concept of “International Toxic Equivalents” (TEQ) has been developed.

The “**Toxic Equivalent**” (TEQ) scheme weights the toxicity of the less toxic compounds as fractions of the toxicity of the most toxic TCDD. Each compound is attributed a specific "**Toxic Equivalency Factor**" (TEF). This factor indicates the degree of toxicity compared to 2,3,7,8-TCDD, which is given a reference value of 1.

To calculate the total TCDD toxic equivalent (TEQ) of a dioxin mixture, the amounts of each toxic compound are multiplied with their Toxic Equivalency Factor (TEF) and then added together.

The TEQ scheme refers only to adverse effects (e.g. cancer) following interactions with the cellular Ah receptors. Other toxic effects of dioxins and dioxin-like compounds are not quantified by this method. Toxic Equivalency Factor (TEF) values vary for different animal species.

**Two schemes:**

1) **I-TEF and I-TEQ**: The older International Toxic Equivalent (I-TEQ) scheme by the North Atlantic Treaty Organisation (NATO) initially set up in 1989 and later extended and updated.

2) **WHO-TEF and WHO-TEQ** (also referred to as TEF or TEQ): More recently, the World Health Organization (WHO) suggested modified Toxic Equivalency Factor (TEF) values (see level 3, question 5.3.1, table 3 WHO-TEFs for human risk assessment).

On average, the result of TEQ-calculations is about 10% higher when I-TEFs are used compared to when WHO-TEFs are used.

References to I-TEQ or TEQ are sometimes omitted when figures are given in a text, which makes it impossible to know which TEF values have been used.

See also question 5.3. How are dioxin mixtures accounted for?