The risk of contamination of food with toxic substances present in animal feed

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Abstract

Toxic substances such as dioxins, mycotoxins, heavy metals, pesticides, veterinary drugs and polycyclic aromatic hydrocarbons are almost ubiquitous in the environment. Thus, they are also present in ingredients for animal feed. Adequate risk management depends on knowledge of absorption, metabolism, carry-over and toxicological profile of these substances and on practical measures to reduce especially the latter two. Generally, toxic substances are metabolized before or after absorption through the intestinal tract. Depending on their physico-chemical characteristics, some substances are metabolized into naturally occurring and generally harmless constituents. Most veterinary drugs and feed additives fall into this group. Other substances are persistent and remain in the animal and in animal products, like dioxins. Heavy metals are not metabolized at all. Some metals irreversibly are bound to body tissues, e.g. lead to bone or cadmium to kidneys.

This review updates the information on carry-over of toxic substances from feed to food of animal origin (meat, organs, milk and eggs). This update is necessary and essential as exposure levels have dropped considerably and analytical as well as toxicological techniques have become much more sensitive. However, simple and cheap analytical techniques to check all suspect feeds or feedstuffs for all possible contaminants are not available. Furthermore, to improve risk management in the field of human nutrition, appropriate data on management and control of toxic substances in animal production chains are essential. The control of environmental contaminants that may cause residues in food of

Abbreviations: 2,4-D, 2,4-dichlorophenoxyacetic acid; DDE, 1,1-dichloro-2,2-bis(p-chlorophenyl) ethylene; DDT, 1,1,1-trichloro-2,2-bis(p-chlorophenyl) ethane; EFSA, European Food Safety Authority; GAP, good agricultural practice; GMP, good manufacturing practice; HACCP, hazard analysis and critical control points; HCB, hexachlorobenzene; HCH, hexachlorocyclohexane; MRL, maximum residue limit; PAH, polycyclic aromatic hydrocarbons; PCB, polychlorinated biphenyls; TEQ, toxicity equivalent

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animal origin is sometimes quite difficult and expensive and is addressed with special attention in this review.
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**Keywords:** Carry-over; Pesticides; Dioxins; Mycotoxins; Veterinary drugs; Heavy metals; Polycyclic aromatic hydrocarbons; Risk management; Feed; Food

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**1. Introduction**

Most components of animal feed are digested as well as absorbed during passage through the intestinal tract. Animal nutrition focuses on those components, which have a nutritive or positive value for the animal. Digestion and absorption of nutritive components have been extensively studied. In contrast, digestion and absorption in the animal is often not considered for toxic – unwanted – substances such as dioxins, mycotoxins, heavy metals, pesticides, veterinary drugs and polycyclic aromatic hydrocarbons, although they are often analysed in both feed and animal products. Some scientists assume complete absorption of these noxious substances, as a worst-case scenario to predict residues in animal products from those in feed. By doing so, they ignore the physiological processes occurring during transit through the intestine and after absorption into the general circulation as well as intermediary metabolism. Furthermore this approach does not take advantage of existing knowledge to identify or implement possible control points for reduction of levels of residues in animal products.

Toxico-kinetic data with emphasis on the physiological processes occurring in animals are, whenever available, the key focus point of the discussion, in order to allow meaningful predictions for situations not directly covered by existing data. The review will focus on data published during the last 10–15 years. Good reviews for older data are available and some older data might have become obsolete due to much lower exposure levels and much improved analytical and toxicological methodology since 1970 or 1980. The concentrations of toxic substances tested in the different experiments are often a reflection of worst-case scenarios for exposure. Thus, the exposure is often quite high and effects measured may be expected to be less confounded by background scatter.

Critical reviews in this area such as those of Biehl and Buck (1987), Heeschen and Blüthgen (2004) and Kan (1994, 2002) are not duplicated. Wherever possible information on risk management or measures to be taken into account in a hazard analysis and critical control points (HACCP) approach are mentioned. The different substances are discussed in groups of related substances and, where appropriate, by animal species.

**2. Chlorinated pesticides and environmental contaminants**

The data on carry-over percentage (amount excreted per day via milk or eggs or deposited in the animal/amount ingested per day on a percentage basis) or concentration ratio (concentration in product/concentration in feed) as well as half-life of these compounds (if reported or to be deduced) are summarized in alphabetical order in **Table 1**. The majority of the data
<table>
<thead>
<tr>
<th>Pesticide</th>
<th>Species</th>
<th>Dose</th>
<th>Duration</th>
<th>Carry-over percentage</th>
<th>Concentration ratio</th>
<th>Half-life</th>
<th>Reference</th>
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<tbody>
<tr>
<td></td>
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<td></td>
<td>Milk/egg Body fat</td>
<td>Milk (fat basis) or egg (whole egg basis)</td>
<td>Body fat (fat basis)</td>
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<tr>
<td>Chlorpyrifos</td>
<td>Cow</td>
<td>0.3–30 mg/kg feed</td>
<td>2 weeks</td>
<td>0.003</td>
<td>&lt;3 days</td>
<td>McKellar et al. (1976)</td>
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<tr>
<td></td>
<td>Laying hen</td>
<td>0.009–0.054 mg/kg BW</td>
<td>6 weeks</td>
<td>&lt;0.001</td>
<td>0.0007</td>
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<td></td>
<td>Pig</td>
<td>19 mg/kg BW “pour on”</td>
<td>9 days</td>
<td>0.018–0.14</td>
<td>&lt;4 days</td>
<td>Schenck and Donoghue (2000)</td>
<td></td>
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<tr>
<td>2,4-D</td>
<td>Goat</td>
<td>23 mg/kg BW equivalent to 480 mg/kg feed</td>
<td>3 days</td>
<td>0.024</td>
<td>0.016</td>
<td>Ivey and Palmer (1979)</td>
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<td>Laying hen</td>
<td>1.4 mg/kg BW equivalent to 18 mg/kg feed</td>
<td>7 days</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
<td>Barnekow et al. (2001)</td>
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<tr>
<td>DDT/DDE</td>
<td>Cow</td>
<td>0.02–4 mg/kg feed</td>
<td>60 days</td>
<td>0.0016</td>
<td>0.05–0.5</td>
<td>7 days</td>
<td>Biehl and Buck (1987)</td>
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<td></td>
<td>Laying hen</td>
<td>100 mg/day per animal</td>
<td>20 days</td>
<td>40</td>
<td>4–80</td>
<td>Nath et al. (1998)</td>
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<td></td>
<td>Laying hen</td>
<td>0.1–1 mg/kg feed 5–90 mg single dose</td>
<td>16–60 weeks</td>
<td>7.8</td>
<td>1.0–1.6</td>
<td>49 days</td>
<td>Biehl and Buck (1987)</td>
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<tr>
<td></td>
<td>Broiler</td>
<td>0.1–1 mg/kg</td>
<td>6 weeks</td>
<td>50</td>
<td>6.4–9.5</td>
<td>49 days</td>
<td>Biehl and Buck (1987)</td>
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<td>Deltamethrin</td>
<td>Cow</td>
<td>2–20 mg/kg feed 10 mg/kg BW</td>
<td>3 days</td>
<td>0.4–1.6</td>
<td>0.4–1.6</td>
<td>1 day</td>
<td>Akhtar et al. (1992)</td>
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<td></td>
<td>Laying hen</td>
<td>7.5 mg per animal 1 mg/kg feed</td>
<td>3 days</td>
<td>0.4–1.6</td>
<td>&lt;0.002</td>
<td>Akhtar et al. (1986)</td>
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<td></td>
<td>Broiler</td>
<td>1 mg/kg feed</td>
<td>70 days</td>
<td>&lt;0.003</td>
<td>&lt;0.003</td>
<td>Akhtar et al. (1985)</td>
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<tr>
<td></td>
<td>Broiler</td>
<td>1 mg/kg feed</td>
<td>70 days</td>
<td>&lt;0.003</td>
<td>&lt;0.003</td>
<td>Marti-Mestres et al. (1995)</td>
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<tr>
<td>Pesticide</td>
<td>Species</td>
<td>Concentration</td>
<td>Exposure Period</td>
<td>Tolerance</td>
<td>Reference(s)</td>
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<td><strong>Diazinon</strong></td>
<td>Cow</td>
<td>0.05–40 mg/kg feed</td>
<td>0.39</td>
<td>&lt;2 days</td>
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<td></td>
<td>Sheep</td>
<td></td>
<td></td>
<td>&lt;3 days</td>
<td>Naidenov et al. (1984)</td>
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<td><strong>Dieldrin/aldrin</strong></td>
<td>Cow</td>
<td>0.05–0.25 mg/kg feed</td>
<td>0.07</td>
<td>22 days for milk, 85 days for heifer</td>
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<td>Laying hen</td>
<td>0.025–0.25 mg/kg feed</td>
<td>18–40</td>
<td>14–17</td>
<td>Blüthgen (2000)</td>
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<td>0.025–0.25 mg/kg feed</td>
<td>60</td>
<td>6 weeks</td>
<td>Kan (1978)</td>
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<td>Broiler</td>
<td>0.025–0.25 mg/kg feed</td>
<td>11</td>
<td>49 days for hens</td>
<td>Biehl and Buck (1987)</td>
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<td><strong>Endrin</strong></td>
<td>Cow</td>
<td>0.05–0.3 mg/kg feed</td>
<td>0.07</td>
<td>16–60 weeks</td>
<td>Biehl and Buck (1987)</td>
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<td>Laying hen</td>
<td>0.025–0.25 mg/kg feed</td>
<td>11</td>
<td>14–17</td>
<td>Kan (1978)</td>
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<td></td>
<td>Broiler</td>
<td>0.025–0.25 mg/kg feed</td>
<td>11</td>
<td>7–10</td>
<td>Kan (1978)</td>
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<td><strong>Endosulfan</strong></td>
<td>Cow</td>
<td>50 mg/cow/day</td>
<td>0</td>
<td>60</td>
<td>Kan (1978)</td>
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<td>Laying hen</td>
<td>0.1 mg injection 5 times</td>
<td>&lt;0.2</td>
<td>1.1–1.9</td>
<td>Biehl and Buck (1987)</td>
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<td>13–19</td>
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<td>60</td>
<td>11</td>
<td>Kan (1978)</td>
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<td><strong>Hexachlorobenzene</strong></td>
<td>Cow</td>
<td>0.01–0.1 mg/kg feed</td>
<td>&lt;79</td>
<td>0.1–1.9</td>
<td>Biehl and Buck (1987)</td>
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<td></td>
<td>Laying hen</td>
<td>0.01–0.1 mg/kg feed</td>
<td>55</td>
<td>13–19</td>
<td>Blüthgen (2000)</td>
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<tr>
<td></td>
<td>Broiler</td>
<td>0.01–0.1 mg/kg feed</td>
<td>&lt;1–21</td>
<td>11</td>
<td>Kan (1978)</td>
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<tr>
<td></td>
<td>Broiler</td>
<td>0.01–0.1 mg/kg feed</td>
<td>8</td>
<td>7–8 weeks</td>
<td>Kan (1978)</td>
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<tr>
<td><strong>α HCH</strong></td>
<td>Cow</td>
<td>0.05–0.5 mg/kg feed</td>
<td>&lt;1–21</td>
<td>0.1–0.2</td>
<td>Biehl and Buck (1987)</td>
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<td>Laying hen</td>
<td>0.05–0.5 mg/kg feed</td>
<td>8</td>
<td>1.8–2</td>
<td>Blüthgen (2000)</td>
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<td>Broiler</td>
<td>0.05–0.5 mg/kg feed</td>
<td>&lt;1–21</td>
<td>3</td>
<td>Kan (1978)</td>
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<td></td>
<td>Broiler</td>
<td>0.05–0.5 mg/kg feed</td>
<td>8</td>
<td>1.5–2 weeks</td>
<td>Kan (1978)</td>
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<tr>
<td><strong>β HCH</strong></td>
<td>Cow</td>
<td>0.05–0.5 mg/kg feed</td>
<td>15–54</td>
<td>1.3–2.3</td>
<td>Biehl and Buck (1987)</td>
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<td>Laying hen</td>
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<td>70</td>
<td>15–25</td>
<td>Blüthgen (2000)</td>
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<td>0.05–0.5 mg/kg feed</td>
<td>70</td>
<td>14</td>
<td>Kan (1978)</td>
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<td></td>
<td>Broiler</td>
<td>0.05–0.5 mg/kg feed</td>
<td>16</td>
<td>7 weeks</td>
<td>Kan (1978)</td>
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<td><strong>γ HCH (lindane)</strong></td>
<td>Cow</td>
<td>0.05–0.3 mg/kg feed</td>
<td>2–4</td>
<td>0.04</td>
<td>Biehl and Buck (1987)</td>
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<td>2–4</td>
<td>0.13–0.2</td>
<td>Blüthgen (2000)</td>
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<td></td>
<td>Broiler</td>
<td>0.05–0.3 mg/kg feed</td>
<td>16</td>
<td>1.8–2</td>
<td>Nath et al. (1998)</td>
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<td>Broiler</td>
<td>0.05–0.3 mg/kg feed</td>
<td>9</td>
<td>1.5–2 weeks</td>
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<td>0.05–0.3 mg/kg feed</td>
<td>2</td>
<td>1.5–2 weeks</td>
<td>Kan (1978)</td>
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<tr>
<td>Pesticide</td>
<td>Species</td>
<td>Dose</td>
<td>Duration</td>
<td>Carry-over percentage</td>
<td>Concentration ratio</td>
<td>Half-life</td>
<td>Reference</td>
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<tr>
<td>Heptachlor (epoxide)</td>
<td>Cow</td>
<td>0.005–0.3 mg/kg feed</td>
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<td>0.5–5</td>
<td>0.02–0.9</td>
<td>Biehl and Buck (1987) Blüthgen (2000)</td>
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<td>Laying hen</td>
<td>0.025–0.25 mg/kg feed</td>
<td>16–60 weeks</td>
<td>35</td>
<td>0.5–0.7</td>
<td>6–7</td>
<td>5–6 weeks Kan (1978) Hsu et al. (1995) Kan (1978)</td>
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<td>Broiler</td>
<td>0.025–0.25 mg/kg feed</td>
<td>6 weeks</td>
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<td>Methoxychlor</td>
<td>Cow</td>
<td>800–7000 mg/kg feed</td>
<td></td>
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<td>&lt;0.5</td>
<td>0.00023</td>
<td>Biehl and Buck (1987) Blüthgen (2000) Schenck and Donoghue (2000)</td>
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<td></td>
<td>Laying hen</td>
<td>2 mg/kg BW equivalent to 0.017 mg/kg feed</td>
<td>2 days</td>
<td>nd</td>
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<td>PCB</td>
<td>Cow</td>
<td>0.07 ng TEQ/kg feed</td>
<td>40 days</td>
<td>2–70</td>
<td>10.5</td>
<td>6.7 days α phase; 87 days β phase Huwe and Smith (2005)</td>
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<td></td>
<td></td>
<td>14.4–31.7 μg/kg feed</td>
<td>56 days</td>
<td>5–84</td>
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<td>10–80 μg/kg feed</td>
<td>24 weeks</td>
<td>5–90</td>
<td>0.09–2.2</td>
<td>1–18</td>
<td>24 to &gt;100 days for fat 30 to &gt;100 days for egg</td>
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<td>Pig</td>
<td>Broiler</td>
<td>3.8 ng TEQ/kg feed</td>
<td>7 days</td>
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<td>0.1–1.1</td>
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<td>Pig</td>
<td>1.5–6 μg/kg feed</td>
<td>3–4 weeks</td>
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<td>5–6</td>
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<tr>
<td>Polychlorinated dioxins/furans</td>
<td>Cow</td>
<td>&lt;1–60</td>
<td>0.018 ng TEQ/kg BW</td>
<td>24 days</td>
<td>0–50</td>
<td>Blüthgen (2000)</td>
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<td>0.014 ng TEQ/kg BW</td>
<td>1 year</td>
<td>1–50</td>
<td>McLachlan and Richter (1998)</td>
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<td>100 ng/kg feed</td>
<td>120 days</td>
<td>30–50</td>
<td>Schuler et al. (1997a,b)</td>
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<td>2.3 ng TEQ/kg feed</td>
<td>4 weeks</td>
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<td>Feil et al. (2000)</td>
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<td>Capsules with PCP</td>
<td>28–58 days</td>
<td>0.3–66</td>
<td>Traag et al. (1999)</td>
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<td>treated wood</td>
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<td>0.2–18</td>
<td>Fries et al. (2002)</td>
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<td>0.13–0.22 ng/kg</td>
<td>6 months</td>
<td>1–60</td>
<td>Lorber et al. (2000)</td>
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<td>5.7 ng TEQ/kg feed</td>
<td>40 days</td>
<td>16</td>
<td>Huwe and Smith (2005)</td>
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<td>Laying hen</td>
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<td>0.97–2.04 ng TEQ/kg feed</td>
<td>56 days</td>
<td>5–48</td>
<td>Hoogenboom et al. (2006)</td>
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<td>6 weeks</td>
<td>3.8–13</td>
<td>3.1–20</td>
<td>Pirard and De Pauw (2005)</td>
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<td>Broiler</td>
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<td>48 ng TEQ/kg feed</td>
<td>7 days</td>
<td>0.3–3.1</td>
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<td>Pig</td>
<td></td>
<td>1–4 g TEQ/kg feed</td>
<td>6 weeks</td>
<td>4.2–4.5</td>
<td>Iben et al. (2003)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>48 ng TEQ/kg feed</td>
<td>7 days</td>
<td>0.1–1.4</td>
<td>Hoogenboom et al. (2004)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.75–4 ng TEQ/kg</td>
<td>11 weeks</td>
<td>1.4–2</td>
<td>Spitaler et al. (2005)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxaphene</td>
<td>Cow</td>
<td>20–140 mg/kg feed</td>
<td>0.014</td>
<td>0.014</td>
<td>Biehl and Buck (1987)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Laying hen</td>
<td>0.1–5 mg/kg feed</td>
<td>38 weeks</td>
<td>0.7–1.1</td>
<td>Ueberschärf et al. (2001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.1–5 mg/kg feed</td>
<td>38 weeks</td>
<td>1.5–17</td>
<td>Schwind et al. (1998)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Broiler</td>
<td>0.1–5 mg/kg feed</td>
<td>5 weeks</td>
<td>1.6–27</td>
<td>Ueberschär et al. (2001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pig</td>
<td>0.01–10 mg/kg feed</td>
<td>90 days</td>
<td>6–16</td>
<td>Jira et al. (2001)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
are on milk and eggs as changes in residue contents in the product during the exposure to the contaminant are easily measured in these products. Construction of a time-related residue profile in meat-type animals requires either sequential slaughtering or frequent sampling by tissue biopsies. Interpretation of these profiles, if available, is not very easy and is further hampered by dilution to growth and changes in body composition during growth.

Overall, the compounds can be divided into three major classes: (1) compounds rapidly metabolized and excreted, an example being chlorpyrifos; (2) compounds with detectable accumulation in the animal, an example being lindane; (3) compounds with high accumulation in the animal, an example being DDT. The data in Table 1 are discussed according to this division. Exposure to contaminants will not always have been sufficient to result in a plateau value (allowing one to calculate reliable concentration ratios) but this information is often lacking, therefore the available data were used. The compilation given in Table 1 is also not sufficient to construct kinetic models for all of the different compounds. Detailed information from the individual experiments has to be used for that purpose. Kinetic models are essential in making reliable predictions of residues to be expected from a limited data set. This situation often occurs during a crisis with contaminants in feed or the environment. van Eijkeren et al. (2006) have recently described such a kinetic model for dioxins and PCBs in laying hens. The problems with dioxins in a potato by-product fed to dairy cows, represent one example in which a kinetic model (based on Derks et al., 1994) was successfully used to predict residue levels in milk after cessation of feeding the product (Hoogenboom et al., 2005).

2.1. Rapidly metabolized compounds

2.1.1. Chlorpyrifos (methyl)

McKellar et al. (1976) fed chlorpyrifos to dairy cattle for 2 weeks. The parent compound and two (oxidized and hydroxylated) metabolites were found at low levels in milk and cream (fat) and the concentrations of all three compounds decreased rapidly after cessation of administration. Johnson et al. (1974) obtained similar results and Hamann et al. (1984) detected chlorpyrifos in milk after application of the pesticide via both skin and air. Hsu et al. (1995) recovered a maximum of 0.14% of intake via the eggs and depletion of residues from the body was rapid. Schenck and Donoghue (2000) obtained similar results in a study with laying hens. Mann et al. (1973) kept turkeys on soil treated with chlorpyrifos. Residues of chlorpyrifos and the two metabolites mentioned above could be found later in skin, liver and kidney of the birds. Ivey and Palmer (1979) treated the skin of pigs with chlorpyrifos and could not detect residues after 3 weeks post-treatment.

These results show that chlorpyrifos has a low persistency in animals but residues in animal products do not necessarily originate solely from feed. Transfer from feed to tissue is low and depletion of residues of parent compound and two metabolites from the body occurs rapidly.

2.1.2. 2,4-Dichlorophenoxyacetic acid (2,4-D)

Barnekow et al. (2001) recently confirmed that after oral administration 2,4-D to laying hens and goats less than 0.1% of the administered dose could be recovered
from edible tissues, milk and eggs. Furthermore depletion of residues occurred within 1 day.

2.1.3. Deltamethrin

Deltamethrin was fed to dairy cattle and depletion in milk after cessation was rapid, indicating a half-life time of about 1 day (Akhtar et al., 1992). These data correspond to low excretion by milk after a “pour-on” application and low excretion in milk of the 14C label of orally given (specifically labelled) deltamethrin (Akhtar et al., 1986; Venant et al., 1990) as well as absence of residues after dermal treatment as reported by Szerletics et al. (2000). Marti-Mestres et al. (1995) fed laying hens deltamethrin and reported no residues in eggs and low levels in tissues. These results are in accordance with the very low recovery of radioactivity in tissues after feeding specifically 14C labelled deltamethrin to laying hens (Akhtar et al., 1985).

Thus, deltamethrin shows low or no carry-over from feed to animal product and is excreted very rapidly.

2.1.4. Diazinon

Lloyd and Matthysse (1971) were unable to detect diazinon in milk of dairy cows after feeding diazinon via a protein supplement. Szerletics et al. (2000) and Naidenov et al. (1984) reported low amounts (<0.025–1 mg/kg) in milk the first day after treatment of cattle and sheep with diazinon. Diazinon thus can occur in animal products after exposure of animals, but excretion occurs quite rapidly within a few days.

2.1.5. Endosulfan

Nath et al. (2000) were unable to detect endosulfan in milk of dairy cows after feeding it for 4 weeks. Even during a case of endosulfan intoxication in cows, the levels of endosulfan in milk remained low and half-life time was less than 4 days (Braun and Lobb, 1976). Transfer of endosulfan injected in layers to eggs was also low (<0.2% of the dose) (Bargar et al., 2001). Metabolism of endosulfan in warm-blooded animals thus appears to be extensive. More information on endosulfan and the low bioaccumulation of the compound can be found in a recent EFSA report (EFSA, 2005d).

2.1.6. Methoxychlor

Old data reported by Blüthgen (2000) and Biehl and Buck (1987) for milk and by Kan (1978) for poultry and eggs all indicate a rapid metabolism and very low accumulation of methoxychlor in animals. Schenck and Donoghue (2000) recently confirmed with a modern, more sensitive, GLC technique, that carry-over of methoxychlor to eggs was absent or very low.

2.1.7. Risk management

These compounds can be found during or shortly after exposure of the animals. The risks for residues in animal products are considered to be quite limited and no special risk management for these rapidly metabolized compounds appears to be necessary. Potential risks for animal health, on the other hand, are sometimes present, depending on the toxicological profile of the compound and the exposure level.
2.2. Compounds with detectable accumulation

2.2.1. Chlordane

Dorough and Hemken (1973) fed different amounts of chlordane during 60 days to dairy cattle. Plateau levels in milk were reached after 10–45 days but no linear dose–response relationship between dosage and residue level in milk was found. The concentration ratio (feed concentration/milk fat concentration) varied between 0.05 and 0.5. As only one cow was tested per dose level, individual variability could not be separated from possible dose-related effects in accumulation and clearance. Pesticide levels in milk fat and body fat were reduced after cessation of administration and metabolism to oxychlordane proceeded rapidly. Half-life was estimated to be about 1 week.

2.2.2. $\alpha$ hexachlorocyclohexane ($\alpha$ HCH)

2.2.2.1. Milk. Bettin (1983) reported a 9.5% carry-over from feed to milk, which is somewhat higher than the value of around 5% reported for buffalo milk (Kapoor and Kalra, 1997). In sheep a carry-over of 4.3% from feed to milk was reported (Froc and Hascoet, 1973). All data fall within the wide range (<1 to 21%) of carry-over data given in the review by Blüthgen (2000).

2.2.2.2. Poultry and eggs. The limited data for $\alpha$ HCH in poultry (Kan, 1978) all indicate a rather low accumulation in both fat and eggs (fat/feed ratio 1–3, egg/feed ratio 0.1–0.2) and low persistence. Thus, $\alpha$ HCH does not accumulate appreciably and the half-life of residues is about 1.5 weeks.

2.2.3. $\gamma$ hexachlorocyclohexane (lindane)

2.2.3.1. Milk. Blüthgen (2000) reported a carry-over percentage for lindane from feed to milk of 2–4%. This range is in accordance with all other data with the exception of 16% reported by Nath et al. (1998). No obvious explanation is available for this high value. The carry-over percentage reported for sheep (Froc and Hascoet, 1973) is 1.5%. The carry-over percentage for milk reported by Biehl and Buck (1987) is in accordance with a rather low carry-over.

2.2.3.2. Poultry and eggs. The data for lindane in poultry (Kan, 1978) all indicate a rather low carry-over in fat and eggs (fat/feed ratio around 2, egg/feed ratio 0.1–0.2) and persistence. Thus, $\gamma$ HCH does not accumulate appreciably and the half-life of residues is about 1.5 weeks.

2.2.4. Risk management

These compounds can be found for some weeks after exposure of the animals. The risks for residues in animal products are considered to be limited and residues are often not found in surveys (e.g. Kan, 2004). This is due to restrictions on the use of most of these compounds in Europe and the USA. For these compounds, the risk management can consist of regular checking of feed ingredients from those areas in the world where the compounds are still in use. The restricted use in most western countries also limits the possible threat they might pose to animal health.
2.3. Compounds with high accumulation

2.3.1. DDT/DDE

DDT and DDE are probably the most studied chemicals in regard to the transfer from feed to food. The metabolism from DDT to mainly DDE and DDD complicates establishment of exact numerical relationships. Most authors report data for total DDT which generally includes DDE, but others occasionally include data for DDD and other metabolites also. This causes some extra variation in reported results. The data cited below are taken from the available reviews.

2.3.1.1. Milk. Blüthgen (2000) reported very different carry-over percentages from feed to milk for DDT (4%) and DDE (80%). The data were apparently restricted to carry-over of the parent compound only. The results were similar to those relating to the excretion of DDT reported by Fries et al. (1971) and Nath et al. (1998). Biehl and Buck (1987) used the concentration ratio feed/milk and reported very different ratios for DDT by direct feeding (0.03) of pure DDT as opposed to “weathered” DDT (0.15–1.08). This difference was probably due to DDE being present in the “weathered” situation in an undefined ratio to DDT and being degraded much more slowly.

2.3.1.2. Poultry and eggs. Kan (1978) reviewed available carry-over data for DDT from feed to poultry and eggs. Concentration ratios (level in fat/level in feed) from feed to fat were lower in high-producing laying hens than in meat-type broiler breeder stock. The excretion of DDT by eggs was probably responsible for this difference, as a higher laying percentage seemed to result in a lower concentration ratio. Carry-over of DDT from feed to egg was similar to carry-over to body fat, but was also influenced by laying percentage. Thus, accumulation of DDT and DDE is considerable and half-life of residues is estimated to be 7 weeks or more.

2.3.2. Dieldrin/aldrin

Dieldrin and aldrin are discussed together as aldrin is metabolized by the animal to dieldrin. Blüthgen (2000) reported carry-over percentages from feed to milk of between 18 and 40%. This rather wide range is probably due to variation between experiments. The concentration ratio milk/feed for both aldrin and dieldrin is 0.39 according Biehl and Buck (1987). Kan (1978) also reported diverging concentration ratios in laying hens and especially in broilers. The data considered to be the most reliable are given in Table 1. Concentration ratios in the literature for dieldrin/aldrin in eggs did not differ to the same extent. Data reported on accumulation in sheep (Froc and Hascoet, 1973) confirm the rather persistent nature of dieldrin in animals, with half-life often exceeding 6 weeks.

2.3.3. Endrin

The carry-over of endrin has not been studied extensively. Biehl and Buck (1987) reported a concentration ratio of milk/diet of 0.07 and Kan (1978) reported concentration ratios for both eggs and abdominal fat of 7–10. These data indicate a somewhat lower accumulation than the related compounds aldrin and dieldrin.
2.3.4. Hexachlorobenzene (HCB)

2.3.4.1. Milk. Blüthgen (2000) reported a carry-over percentage from feed to milk of less than 79%, but no range was reported. Older data (Goursaud, 1976; Rohleder et al., 1976) indicated a lower carry-over percentages from feed to milk for HCB. The carry-over percentage for sheep milk was reported to be 6.5% (Froc and Hascoet, 1973).

2.3.4.2. Poultry and eggs. Most reported concentration ratios of HCB in poultry and eggs are in the range of 10–20 (fat/feed ratio) or 1–2 (egg/feed ratio) (Kan, 1978). All data support the persistent nature of HCB in animal tissues, a rather high accumulation and a half-life time of about 7 weeks.

2.3.5. \( \beta \) hexachlorocyclohexane (\( \beta \) HCH)

2.3.5.1. Milk. The rather persistent nature of the \( \beta \) isomer has been well demonstrated. Carry-over percentages up to 100% have been reported (Heeschen et al., 1983), but generally values between 15 and 55% are reported (Blüthgen, 2000). For sheep, carry-over from feed to milk is reported to be 13% (Froc and Hascoet, 1973).

2.3.5.2. Poultry and eggs. The limited data for \( \beta \) HCH in poultry (Kan, 1978) indicate a rather high accumulation (concentration ratio fat/feed 14–25, 1.3–2.3 for egg/feed) and high persistence with a half-life of 7 weeks.

2.3.6. Heptachlor (epoxide)

Heptachlor is converted in animals to heptachlorepoxide. The residue data used in this review are thus based on heptachlorepoxide as it is not always clear from the literature which compound was fed and in case of the epoxide, which isomer was administered. This contributes to the variation observed in the accumulation data, especially for milk.

2.3.6.1. Milk. Reported carry-over of heptachlor(epoxide) from feed to milk varies between less than 5% (Blüthgen, 2000) and 37% (Hascoet and Kerhoas, 1972). The carry-over to milk of sheep was reported to be 15% (Froc and Hascoet, 1973). Biehl and Buck (1987) reported a concentration ratio milk/feed of 0.2–0.9 for heptachlorepoxide and of 0.02 for heptachlor.

2.3.6.2. Poultry and eggs. Heptachlor seems to accumulate less when fed as such than when the epoxide is fed (Kan, 1978). The concentration ratios vary generally between 3 and 7 for the parent compound and 10 and 20 for the epoxide. A half-life of 5 weeks or more for residue depletion has been observed. The absence of precise information on the compound fed precludes further speculation as to factors involved in the differences observed between trials.

2.3.7. Risk management

These compounds can be found in animal products for weeks or months after exposure of the animals. The risks are nevertheless considered to be limited. Residues found in surveys generally do not exceed MRL levels (e.g. Kan, 2004). Use of most of these compounds is not (anymore) allowed in Europe and the USA. The risk management for these compounds
should consist of regular checking of feed ingredients from those areas in the world where these compounds are still in use or where previous results have shown contamination to be present. The ban in most western countries also limits the possible threat they might pose to animal health.

2.3.8. Polychlorinated biphenyls (PCBs)

Accumulation, metabolism and depletion of PCBs in (farm) animals have been studied extensively. Reviews by Biehl and Buck (1987), Blüthgen (2000) and Heeschen and Blüthgen (2004) indicate clearly the difference between the individual PCB congeners in pharmacokinetics, with e.g. carry-over percentages from feed to milk ranging between 2 and 70%. The enormous differences in metabolism between different congeners have recently been demonstrated elegantly in a study with mice by Imsilp et al. (2005).

An early study by Hansen et al. (1983) reported concentration ratios in broiler fat of 1–15 for different congeners after a 3-week feeding trial. The overall values for accumulation of total PCBs in the different experimental groups reported in Table 1 differ less. Ueberschär and Vogt (1986) reported somewhat lower concentration ratios for six “indicator” PCBs in broilers but similar values in both fat and egg of laying hens. The concentration ratios recently reported by Hoogenboom et al. (2004) for both broilers and piglets after a 1 week of exposure (probably no plateau achieved), were generally lower and in the 0.1–3 range. The differences in accumulation between congeners within species and between species within congeners were once again marked. The experiments of De Vos et al. (2003, 2005) and Maervoet et al. (2004) with diets containing seven marker PCBs and different oil contents with broilers and layers showed absence of an effect of oil content on absorption and accumulation of PCBs. The overall concentration ratio for the PCBs studied was around 9–11. Hoogenboom et al. (2006) reported carry-over percentages from feed to egg of 5–84% for the different congeners studied. The carry-over percentages from feed to egg for the seven indicator PCBs reported from the studies of De Vos et al. (2005) and Hoogenboom et al. (2006) show a remarkable similarity in magnitude.

2.3.9. Dioxins/dibenzo furans

Residue formation of dioxins and dibenzofurans has attracted a lot of attention in recent years and consequently a number of reviews especially on residues in milk have been published by e.g. Fries (1995), Blüthgen (2000), Heeschen and Blüthgen (2004) and Hoogenboom (2004). This information is not be duplicated here in detail; instead focus is on recent overall data, in some cases not covered in those reviews.

2.3.9.1. Milk. Fries (1995) showed clearly that, within congeners with 4–8 chlorine atoms, increase in number of chlorine atoms leads to reduced excretion of those congeners in milk. Schuler et al. (1997a) estimated from field data the carry-over percentage for a number of dioxins from grass to milk. They also reported a similar relationship between chlorination rate and concentration ratio (concentration in grass relative to that in milk). Similar carry-over percentages reducing from about 40% for the four chlorinated dioxins to 0.5% for the eight chlorinated ones were reported in an experiment by McLachlan and Richter (1998). Persistency of the individual congener is an important feature, the dioxins and dibenzofurans less susceptible to metabolism showing a higher carry-over to milk (Blüthgen, 2000). The
trial of Fries et al. (2002) with dairy cattle showed a mass balance of dioxins above 100% for some dioxins. This apparent “synthesis” of dioxins with seven or eight chlorine atoms indicates, however, that not all aspects of dioxin formation and degradation are yet known.

2.3.9.2. Meat. Feil et al. (2000) fed calves for 120 days on contaminated feed and were able to obtain concentration ratios (level in tissue versus level in feed) for a number of four and five substituted congeners. These factors for the different congeners varied between 0.2 and 11 for fat, depending most probably on rapidity of metabolism. Spitaler et al. (2005) fed pigs with contaminated feed for 12 weeks. They calculated, on a total TEQ basis, a concentration ratio around 1.4 for total chlorinated dioxins and dibenzofurans. Iben et al. (2003) fed broilers on contaminated feed for 6 weeks. Expressed on a total TEQ basis, a concentration ratio around 4.5 can be calculated for total chlorinated dioxins and dibenzofurans. In both studies considerable differences in accumulation were observed between the different congeners. Hoogenboom et al. (2004) fed contaminated feed to young broilers and young pigs for 1 week. The concentration ratios reported varied between 0.1 and 3.1. The variations were both large within species between congeners as well as between species for the same congener.

2.3.10. Eggs

Hoogenboom et al. (2006) fed diets with five different levels of dioxins up to 2.04 ng TEQ/kg to laying hens for 8 weeks. Carry-over percentages from feed to egg ranged from 5 to 48% with a tendency to lower carry-over for the highly chlorinated congeners. Addition of three different mineral type binders to the feed at 5 g/kg did not influence the observed carry-over. The availability of dioxins from contaminated soil fed to laying hens was estimated to be between 40 and 60% as opposed to 80 and 100% availability of dioxins from a solution in oil (van Eijkeren et al., 2006).

2.3.11. Toxaphene

Biehl and Buck (1987) reported an overall concentration ratio milk/feed of 0.014 for toxaphene, indicating a moderate accumulation in dairy cattle. Kaltenecker (2001) reported carry-over percentages for the different congeners in toxaphene from feed to fat in laying hens ranging between 8 and 14%. The percentage of excretion via eggs was estimated to be between 22 and 37% of intake. Jira et al. (2001) also reported on carry-over in laying hens and swine. Their short communication indicated a difference between species in metabolism of the different congeners only, but no quantitative data were reported. Ueberschär et al. (2001) reported concentration ratios of tissue/feed for abdominal fat of poultry ranging from 1.5 to 27 for the different congeners. The ratios for eggs were somewhat lower. Toxaphene has been recently evaluated by EFSA as an undesirable substance in animal feed (EFSA, 2005a). That report contains a good summary of the available information on this substance.

2.3.12. Risk management of chlorinated pesticides and environmental contaminants

Cessation of direct application on animals or presence of persistent compounds in their feed, housing or pasture is logically the first measure to control residues. Prevention of occurrence of residues in products of animal origin (a control point in HACCP) can be achieved via control of levels in (fat containing) feedstuffs. This approach has proven to be
efficacious in reducing residue levels over the past 30 years (e.g. Kan, 2004). Residues of contaminants in products of animal origin due to environmental contamination are harder to control (Kan, 2005). When (legally) acceptable limits for residues have been surpassed, removal of the contaminated items from the human food chain is the only option. The direct and indirect costs involved in these recall and removal operations are often quite substantial.

3. Other organic pollutants in feed and food

Ueberschär and Matthes (2004) fed different doses of chlorinated paraffins to broiler chickens for 31 days. They reported dose-related residues in the different tissues with the highest concentrations in abdominal fat. In total however less than 5% of intake was retained in the body, most of the intake being metabolized or excreted. Mineral oil hydrocarbons are also deposited in fatty tissues of animals, if present in their feed (Grob et al., 2001). These authors found \( n \)-alkanes with chain length from 10 to about 40 C-atoms in both feed and animal products. A balance calculation for laying hens indicated a transfer of these alkanes to eggs of about 2%. Acrylamide is a substance of recent toxicological concern due to its presence in heated (potato) products. Blumenthal et al. (1995) administered a single uniformly \( 14 \) C labeled dose to laying hens and were able to recover up to 0.5% of the label from the eggs. Kienzle et al. (2005) fed laying quail on a diet containing around 2.5 mg/kg acrylamide for 30 days. Less than 0.3% of the dose was excreted in the eggs and more than 94% of the dose could not be accounted for.

Polycyclic aromatic hydrocarbons (PAH) can occur in over-heated agricultural products as well. Indirect human exposure to PAH through carry-over from contaminated feedstuffs to animal products has not been addressed widely. Kan et al. (2003) fed dried grass with a considerably increased PAH content to dairy cattle and were unable to establish whether carry-over to milk occurred. The recent work of Cavret et al. (2003, 2005) showed that both intestinal absorption of PAH and passage through the mammary epithelium occurs for some members of this family. Therefore, the possibility of carry-over to milk should not be ruled out. This would explain the differences in PAH content in milk samples from different regions in both Finland (Hietaniemi, 1996) and the USA (Schaum et al., 2003). Avoidance of the presence of these pollutants in feed is often possible, but their environmental presence is much harder to control. The regime used to manage or control incidents with these pollutants depends heavily on the place, time and magnitude of the problem. A fixed strategy for this kind of problems has not yet been established.

4. Heavy metals

An important feature of heavy metals is that the chemical form in which they are present may change during passage through the intestine or storage in animal tissue, but they are not metabolized. Biehl and Buck (1987) indicated that excessive amounts of metals in animal feed and feedstuffs are often due to human actions. They result from either agricultural or industrial production or through accidental or deliberate misuse. Attention in this review is
on contamination by cadmium, lead and mercury as well as arsenic, although the latter is by definition not a heavy metal. Studies by Vreman et al. (1986) and Kreuzer et al. (1981) showed clearly that muscle and milk are not likely to show high levels of heavy metals when animals are exposed via the diet. Liver and kidney, on the other hand, often show a clear dose–response related increase in heavy metal concentration after dietary exposure.

4.1. Cadmium

Cadmium accumulates mainly in liver and kidney (Prankel et al., 2004). Carry-over to milk is very low or absent (<0.05%) (Blüthgen, 2000). The same is true for carry-over to meat and eggs. Prankel et al. (2004) carried out a meta-analysis on 21 randomized trials with sheep. Three factors proved to be very important in predicting cadmium content of liver and kidney, namely cadmium concentration in the feed, duration of exposure to the feed and the predominant chemical form of cadmium in the feed. All other factors such as sex, age and body weight at start were not significant. Based on this model, Prankel et al. (2005) predicted that in sheep given a diet containing 1 mg/kg cadmium (the legal limit) in organic form, the residues in kidney surpass the legal limit of 1 mg/kg wet weight for kidney after 130 days. The MRL in liver is surpassed after 175 days. If the cadmium in the feed is predominantly in the inorganic form, it takes 2–4 times as long to achieve the same effect. The authors discriminated only between organic and inorganic forms of cadmium. Thus differences in solubility between the different inorganic salts were not taken into account. Those differences have been shown to have a major effect on residues in broilers and layers (Nezel et al., 1981).

4.2. Lead

Biehl and Buck (1987) state that: “Foods of animal origin do not usually have excessive lead concentrations”. Animal tissues with the highest concentrations are liver, kidney and bone and lead concentrations in milk are usually much lower than blood levels. Blüthgen (2000) reported a carry-over percentage from feed to milk of 0.1–1%.

4.3. Mercury

Alkylmercury compounds tend to accumulate in skeletal muscles and brain, whereas aryl compounds and inorganic mercury salts accumulate in liver and kidneys (Biehl and Buck, 1987). Due to the cessation of use of organic mercury compounds as fungicides, levels in feedstuffs have dropped considerably over the years. Blüthgen (Blüthgen, 2000) reported a carry-over of less than 0.1% from feed to milk.

4.4. Arsenic

EFSA (2005b) has recently evaluated arsenic as an undesirable contaminant in animal feedingstuffs. Several statements in that report seem pertinent here namely: “Arsenic is a naturally occurring element”. “An assessment of the levels of exposure of farm animals to individual arsenic compounds is not possible because the majority of data on feed materials
are reported as total arsenic”. “In mammalian species (and poultry), inorganic arsenic is converted into methylated metabolites, which are rapidly excreted compared to other organic arsenic compounds. Hence the carry-over of arsenic compounds from feeds to edible tissues of mammalian species and poultry is very low”. Thus although some caution is warranted, no major concerns on arsenic in feed seem necessary.

4.5. Risks and risk management

The HACCP approach suggests the following: reduction of exposure via feed is relatively easy by avoiding the use of certain contaminated feedstuffs. However, environmental and incidental exposure is hard to control. Checks on levels of heavy metals in animal products are generally conducted on a survey basis and prevention of occurrence of products with violative levels of heavy metals seldom or never occurs (Kan, 2002).

5. Mycotoxins

Mycotoxins in feed and their transfer to foodstuffs of animal origin as well as the strategies to prevent occurrence of adverse effects have been outlined in other reports and in other papers in this Special Issue. Galvano et al. (2005) e.g. discussed the effects of mycotoxins in the human food chain. All aspects of exposure through the diet were covered in their review. The fate of mycotoxins was specifically discussed by Yiannikouris and Jouany (2002). General reviews on mycotoxins in feed and their consequences have also been published by EFSA in recent years (2004a,b,c,d, 2005a,c). A few relevant points of interest are noted here.

Carry-over percentage of aflatoxin from feed to milk was long assumed to range between 1 and 2%. Higher values up to 6% have, however, also been reported. EFSA (2004a) has calculated the carry-over percentage to be best represented by the regression equation:

\[
aflatoxin \ M_1 \ (\text{ng/kg milk}) = 10.95 + 0.787 \times (\mu g \text{ aflatoxin B}_1 \ \text{intake per day})
\]

EFSA (2004b,c, 2005c) has concluded that carry-over of deoxynivalenol (DON), zearalenone and fumonisin to products of animal origin is very low. Accumulation of ochratoxin A occurs predominantly in blood, liver and kidney. Muscle, milk and eggs contain much lower ochratoxin levels when the animals are exposed to this mycotoxin (EFSA, 2004d). Numerical relationships have however not been established.

5.1. Risk management

Prevention and control of mycotoxins in the pig and poultry production chain have been described by Dänicke et al. (2000) and Dänicke (2002). Emphasis was laid on prevention during the growing phase of the plants, as removal or inactivation of the toxins often proved to be quite difficult or not economical. Mycotoxin control in the field is – however – quite hard to be executed. Weather conditions play a pivotal role in fungal growth and mycotoxin formation, and can not be controlled. Galvano et al. (2001) concentrated on dietary strategies to counteract the effects of mycotoxins. However the economical and technical feasibility
has still to be established for many suggested strategies, as efficacy under practical conditions is seldom measured or reported. Diaz and Smith (2005) concentrated on sequestering agents to counteract the effect of mycotoxins: some promising products were described. They stress – however – that in vitro tests on binding may not be good predictors for in vivo efficacy. They further warn for generalizations concerning efficacy comparisons between types of animals or mycotoxins.

6. Veterinary drugs and feed additives

Veterinary drugs and feed additives are generally administered to animals on purpose and an adequate withdrawal time is prescribed. From the perspective of HACCP, the critical control point is the farmer or the veterinarian, who is responsible for meeting any legal obligations related to the use of the drug or additive.

Carry-over of drugs or additives from one medicated feed batch to the next non-medicated one during either manufacturing, transport or even at the farm can occur. The critical control points for this chain of events are both in the feed mill and on the farm. Systems such as GMP for feed production and GAP at the farm should ensure that adequate precautions are taken. The reported incidence of coccidiostat residues in eggs in the EU in 2003 (SANCO/2810/2004) does, however, indicate that good control has not yet been achieved.

Kan and Petz (2000) have reviewed several trials in which veterinary drugs or feed additives have been administered to laying hens. Nearly all veterinary drugs and feed additives available on the market and tested may result in residues in eggs, thus inadequate control of contamination of feed may result in residues in eggs exceeding legal limits. As MRL values are not set for non-target animals (thus a “zero” tolerance), any drug not licensed for use in layers if detected in eggs, will constitute a violation of legal limits.

As with for toxin degradation (Biehl and Buck, 1987), livestock are also excellent biodegraders of drugs and additives. Geertsma et al. (1987) e.g. reported that less than 1% of sulfadimidine administered to laying hens was excreted via the egg. Thus, although residues of drugs can be detected rather easily in foodstuffs of animal origin with modern analytical techniques, metabolism is much more important than carry-over, quantitatively. The reported residues, although exceeding detection limits or even MRLs, are often not of major concern for human health. The main notable exception is the presence of clenbuterol or other beta-agonists in liver of illegally treated animals, slaughtered before an appropriate withdrawal time had passed (Barbosa et al., 2005). Attention is therefore focused on eggs and milk which are produced on a daily basis, and withdrawal periods do not apply.

6.1. Milk

Transfer of antibiotics or other veterinary drugs from feed to milk has not been studied to a large extent in contrast to residue studies in milk after injection or dermal application. McEvoy et al. (1999, 2000) fed concentrates containing sulfadiazine, sulfadimidine or chlortetracycline at levels (250 mg/kg) normally used for treatment of pigs and poultry to dairy cattle for 21 days. Peak levels of sulfonamides in milk were in the range around 100 μg/l, which is the European MRL value for sulfonamides. van Rhijn et al. (2000)
fed concentrates containing three low levels of nicarbazin, meticloprindol and ivermectin, respectively, to both high and low-producing dairy cattle for 21 days. The concentrations of the drugs ranged between 1 and 25% of the normal values for therapeutic or prophylactic use. Thus they mimicked concentrations likely to occur due to carry-over in the feed mill. DNC (the persistent component of nicarbazin) could not be detected in milk at all (<25 μg/kg). Very low levels could be detected in the fat of some animals slaughtered after about 8 days of withdrawal. Meticloprindol was found in milk in concentrations between 5 and 50 μg/kg during the feeding period. The amounts found in milk varied, but a dose–response relationship between levels in feed and milk could be observed. Residue levels of meticloprindol in milk dropped to less than 5 μg/kg immediately post-exposure. Ivermectin was found in the milk throughout the whole exposure period and up to 10 days post-exposure. Concentrations found in milk were up to 7 μg/kg. Also a good dose–response relationship between concentrations in feed and those in milk was reported. Blüthgen (2000) reported a carry-over percentage for sulfadimidine from feed to milk of less than 1%. Moreno et al. (2005) administered both oxendazole and albendazole by oral administration to dairy cattle. Oxendazole and oxidized and hydroxylated metabolite concentrations in milk were less than 1 μg/ml. The parent albendazole was not found in milk and the metabolite (sulfoxide and sulfone) concentrations were less than 1 μg/ml.

Hamscher et al. (2004) describe the presence of colchicine in sheep milk due to the consumption of forage containing this alkaloid, also used in veterinary and human medicine. The levels however were too low to result in a pharmacological effect in humans consuming that milk.

6.2. Egg

Kan and Petz (2000) have reviewed several trials in which veterinary drugs or feed additives were administered to laying hens. This review has indicated that nearly all drugs available on the market and tested cause residues in eggs when fed to laying hens. The list of drugs in question on can meanwhile be extended to include the coccidiostats halofuginone (Mulder et al., 2005; Yakkundi et al., 2002) and toltrazuril (Mulder et al., 2005). Generally the levels reported in eggs are low and the carry-over percentage from feed to egg is around or below 1%. However differences in carry-over percentage between drugs have been reported (Furusawa, 2001).

6.3. Risk management

Two main actions should be taken: firstly, adherence to adequate administration and prescribed withdrawal times; and secondly, due attention, when producing and using medicated feeds, to prevent carry-over both in the feed mill and at the farm.

7. Conclusions

Carry-over of toxic substances from feed to food is influenced by absorption, metabolism and excretion of the compound. Absorption and excretion occur both in the intestine and
in other tissues. Measurement in feed and food only obscures the relative contributions of the different processes in the animal and does not reveal the possibilities of intervention in these processes. Possible interventions have been outlined briefly in the respective sections of this paper.

The following actions are possible in general terms:

- Prevention of exposure either through feed or from the environment
- Application of a withdrawal time
- Use of adsorbents to bind toxic substances in the feed
- Manipulation of animal physiology to enhance metabolism or excretion of contaminants from the animal.

Prevention of exposure is by far the preferred risk management tool. Known contaminants from known sources can be handled effectively in this way, the reduction in organochlorine and heavy metal residue levels in poultry over the past 30 years (Kan, 2004) being a clear example. The absence of simple and cheap analytical methods to check for the presence of all possible contaminants in all feedstuffs at the feed mill level causes, unfortunately, this system to fail from time to time as the recent dioxin problems in animal fat in Belgium and the Netherlands have shown.

Withdrawal times should be followed if prescribed legally and may in some instances provide a solution. In the case of milk and eggs, which are produced on a daily basis, the animal products are most likely to show increased residue levels during prolonged exposure. Cessation of exposure is generally not a direct solution as residues will in most cases not fall within 1 day below legal limits. Thus, cows and laying hens will continue to deliver products legally not fit for human consumption, during days or even weeks and these products have to be disposed of. Withdrawal times can be an appropriate solution for growing (meat-type) animals, which do not deliver a product on a daily basis. Reduction in contamination levels, due to dilution as a result of growth will also help to obtain a product in compliance with legal residue limits. Fries (1996) presented a model for prediction of residues or dioxins and pesticides in growing pigs and Hoogenboom et al. (2004) e.g. have presented some data for residues of dioxins in broilers and pigs during a grow-out period. During the most recent dioxin crisis in the Netherlands, the Dutch Food Safety Authority decided that all pigs weighing less than 50 kg were contaminated to such a low extent that they could grow to 110 kg and not exceed the legal limits for dioxins at slaughter (Press communication VWA February 6, 2006).

Use of adsorbents has been tested extensively both for organochlorine compounds and mycotoxins. The results for organochlorine compounds have not been promising (Kan, 1994). Diaz and Smith (2005) pointed out that for mycotoxins there are some promising products, but certainly no general solutions.

Manipulation of animal metabolism e.g. by certain drugs such as thyroid stimulators, additional oil in the diet or repeated cycling of fasting and feeding, has been tested in the past to speed up excretion of organochlorine compounds. The results generally do not encourage application in practice (Kan, 1994).

Concerning the different groups of toxic substances discussed in this review, the following general points can be made. Persistent organohalogen compounds are generally absorbed and translocated efficiently and are not metabolized rapidly. Thus, prevention of
their occurrence in animal feed is the best way of controlling residues. Less persistent compounds are seldom found in animal products as a result of feed contamination. Heavy metal and drug contamination of feeds are also to be controlled at the feed mill, by selection of feed ingredients and through proper manufacturing practices. Mycotoxin control is quite hard to be executed as weather conditions play a pivotal role in fungal growth and mycotoxin formation. Absorbents added to the feed may sometimes alleviate the problem.

Environmental contamination is still a problem for a control and risk management system. Contaminations are generally dealt by on a case by case basis. Risk assessment for consumers plays an important role, as well as economic and feasibility aspects. The absence of simple and cheap analytical methods for detecting most contaminants precludes extensive screening as a tool for risk management.

Despite large numbers of published papers on residues in products of animal origin and carry-over of toxic substances, specific knowledge on the dynamics of turnover in farm animals is still quite scarce. The many empty sections in Table 1 illustrate this point. In some cases old data (not reviewed here) might help to fill the gaps. But in many instances, the experiments have been conducted over too short a period of time or too limited information on intake levels was presented. This precludes their use in dynamic models, capable of handling different situations and making useful predictions. Setting priorities in this huge task is dependent on a long-term view concerning human and animal health issues. The toxicity of compounds, as well as their persistence in the ecosystem, will be of primary importance in the selection process. Incidents with toxic substances in feed and food will, however, also influence the research agenda. Persistent substances, not yet extensively studied in farm animals, such as brominated flame retardants or fluorine-containing products, are very likely to become a priority in the near future.

Information on possible intervention strategies as a risk management tool to be used in a HACCP approach is often lacking. Development of quality systems requires this knowledge and will become another impetus in setting the research agenda.

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**Glossary**

*Carry-over percentage:* Amount excreted per day via milk or eggs or deposited in the animal/amount ingested per day

*Concentration ratio:* Concentration in milk or body fat on fat basis or in egg on whole egg basis/concentration in feed

*Half-life:* Time in which the concentration in milk, fat or egg diminishes to half that in tissue after cessation of administration (given by the authors or estimated from their data)

*Rapidly metabolised:* Compounds that during administration result in measurable levels in tissues but generally not an increase in tissue levels above those in the feed (these compounds often have half-life times of <1–3 days)

*Detectable accumulation:* Compounds that during administration result in tissue levels about or slightly above levels in the feeds; half-life about 1 week

*High accumulation:* Compounds that result in tissue levels well above levels in the feed; half-life well over 1 week