receptor (ER) transfected cell lines, the (anti-)estrogenic activity of these compounds was assessed. In stably transfected 293 Human Embryonal Kidney cell lines compounds show antagonist activity at both ERα and ERβ when competing with estradiol, and no agonist activity. However, in stably transfected U2OS osteoblastic bone cells compounds show agonist activity at ERα and antagonist activity at ERβ. Furthermore, AHTN and HHCB induced teratogenic effects in zebrafish (*Danio rerio*) larvae.

P2E30
Octamethylcyclotetrasiloxane induces estrogenic effects in B6C3F1 mice

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Octamethylcyclotetrasiloxane (D4) is a low molecular weight silicone which is extensively used in personal care products and foods because of its lubricity, low surface tension, and low heat of vaporization. The estrogenic activity of D4 was evaluated in these studies using both in vitro and in vivo methods. Intact female B6C3F1 mice demonstrated a progressive dose dependant decrease in serum estradiol levels following oral exposure to D4 with up to 50% suppression observed following a dose of 1000 mg/kg. Ovariectomized mice showed a dose-dependant increase in uterine weight (up to 3-fold) following D4 exposure which was blocked by pretreatment with the estrogen receptor atangonist ICI 182, 780. Uterine peroxidase activity was also increased in D4 exposed mice. In vitro, D4 at concentrations of 10^{-6} and 10^{-4}M demonstrated dose-dependent competition with ^{3}H-estradiol in an estrogen receptor-α binding assay. These data indicate that D4 has estrogenic activity which may be mediated through estrogen receptors.

P2F
Organ toxicity — skin, gastrointestinal, liver, kidney, cardiovascular, and haematopoietic systems

P2F1
Evaluation of SkinEthic human reconstituted epidermis for percutaneous absorption testing

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The usefulness of SkinEthic reconstituted human epidermis for in vitro percutaneous absorption experiments has been evaluated at Syngenta CTL and TNO Nutrition and Food Research. Penetration of water and 3 reference chemicals through normal human epidermis (NHE) and reconstituted human epidermis (RHE) was measured using established methods and the same batches of RHE. Assessment of skin integrity using tritiated water showed excellent agreement for NHE with mean permeability coefficient (Kp) values of 1.0×10^{-3} and 1.1×10^{-3} cm/h at CTL and TNO, respectively. However, RHE gave abnormally high water Kp values ranging from $32–54 \times 10^{-3}$ at CTL to $16–54 \times 10^{-3}$ cm/h at TNO. Similar values were obtained for individual batches of RHE in each lab with the higher values supported by poorer morphological preservation. Under identical conditions of application, there was very good inter-laboratory agreement in the rates of absorption of caffeine (0.5 and 0.3), testosterone (1.2 and 1.7) and benzoic acid (3.4 and 5.3 ug/cm^2 per h) at CTL and TNO, respectively, using NHE. In contrast, using RHE there were a number of significant inconsistencies between the two laboratories. Absorption was grossly overestimated with RHE for caffeine and benzoic acid with rates, in some cases, more than 10-fold higher than NHE. Testosterone gave very different results in the two labs in terms of both rate and time course absorption profile. Based on these observations we conclude that the SkinEthic RHE, at this stage of development, does not adequately represent the barrier properties of normal ex vivo human epidermis.

P2F2
Effect of glycolic acid on UVB-induced skin irritation and inflammation in guinea pigs

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The objective of this study was to examine the dose (from 1 to 7 mg/cm^2) and time (for up to 14 days) dependent effects of glycolic acid alone or in combination with UVB (0.4 and 3 J/cm^2) on skin damage and inflammatory response in guinea pigs. Glycolic acid increased skin irritation in dose and time-dependent manners, and reduced the stratum corneum integrity without changes in the basic structure of the skin. The higher doses (5 and 7 mg/cm^2) of glycolic acid caused severe skin irritation and 7-mg/cm^2 glycolic acid substantially destroyed the epidermal layer. Glycolic acid also enhanced the UVB-induced skin irritation and the reduction of the stratum corneum integrity. Severe skin irritation and partial destruction of the epidermal layer was also seen in the combination treatment of UVB and lower doses of glycolic acid. However, glycolic acid did not change basal and UVB-induced PGE_2 release and the COX-2 protein expression. These results show that glycolic acid causes skin damage in dose and time dependent manners and enhances the UVB-induced skin damage without accompanying of the release of PGE_2 and COX-2 protein expression.

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Abstracts

Lectures

Deichmann Lecture
Apoptosis and toxicology — What relevance?

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All cells are mortal — i.e. they can be killed if a vital metabolic process is blocked. All cells can engage in a variety of stress responses, such as the heat shock response, when vital processes are slowly, or only partially, inhibited. These stress responses involve detection of the damage, transduction of signals, and activation of a response, such as production of heat shock proteins, proteases, or chaperones. Many cells possess mechanisms whose purpose is to kill the cell. Such physiological cell death mechanisms are used to remove unwanted or damaged cells. Among metazoans, physiological cell death is implemented by a family of cysteine proteases, termed caspases, that exist in a latent state even in healthy cells. Cells killing themselves via activation of their caspases typically exhibit an appearance termed 'apoptosis'. Apoptosis is not only used to remove cells in physiological circumstances, such as during development, but is also a common response to cell stress. Thus many cells will detect damage to, or malfunctioning of, vital metabolic processes, and generate signals that lead to activation of the caspases, and apoptotic death of the cell. This has led to a great deal of confusion, because many drugs and toxins with known biochemical functions have been found to induce apoptosis, and rather than this being interpreted as a stress response, it has often wrongly been assumed that apoptosis is a direct effect of the drug or toxin.

Plenary Lectures

L1
The pathogenesis of prion diseases

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Prion diseases occur because the full length prion protein (PrP) can exist in two conformations: (1) a normal conformation in which the N-terminal half of the molecule has little or no β-sheet, which is characteristic of PrPc; and (2) an abnormal, pathogenic conformation in which the N-terminal half acquires a β-sheet conformation, which is characteristic of PrPSc in scrapie and bovine spongiform encephalopathy (BSE) of animals and Creutzfeldt-Jakob disease (CJD) in humans. The property of the prion protein which gives prion diseases the characteristics of a slow virus infection is the efficient conversion of PrPC into nascent PrPSc when the former physically interacts with 'infecting' PrPSc. Sporadic CJD accounts for 85% of human prion diseases and appears to be initiated by the spontaneous conversion of PrPC to PrPSc (a one per million event). Familial CJD (15%) is caused by mutations of the PRNP gene. The PrPSc in sporadic and familial CJD is infectious. Prion strains are defined by the disease phenotype they produce in a host animal. Conformational dependent immunoassays indicate that the PrPSc comprising each prion strain has a different conformation, possibly as a result of different amounts of β-sheet and different PrPSc polymerization patterns. All of the parameters that define each prion strain can be modified by manipulating the amino acid sequence of PrP, which supports the protein only hypothesis. Finally, neuronal dysfunction and death in prion diseases require both the conversion of PrPC to PrPSc and the accumulation of nascent PrPSc in or on neurons and their processes.

L2
Food and cancer

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Food is an important factor in determining cancer incidence in many countries and regions. Food components relevant to cancer development can be divided into macro- and microcomponents. The former tends to act indirectly. The latter usually has a clearly defined action, for example as genotoxic agents. Food can have both positive (carcinogenic) and nega-

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