APPENDIX 3
Risk assessment report for existing substances

ECETOC / EFOA

Propane, 2-methoxy-2-methyl-

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Information on the rapporteur

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Toxicokinetics
The toxicokinetic properties of MTBE have been studied extensively. It is readily absorbed by all routes of exposure but there are quantitative differences in the extent of absorption. The absorbed material is distributed uniformly in all tissues and shows no tendency to accumulate. This is due to rapid removal of MTBE via exhalation and metabolism. The one exception to this uniform distribution is a species- and sex-specific accumulation which occurs in the male rat kidney – this is explained by the affinity of MTBE for the protein $\alpha 2\mu$-globulin. Metabolism leads to two principal metabolites, ie *tert*-butanol (TBA) and formaldehyde. These are further metabolised and show no tendency to accumulate to any significant extent. TBA excretion proceeds relatively slowly (half-life: 8 hours in humans). Elimination of the products resulting from TBA metabolism occurs mainly via urine. Formaldehyde and products resulting from formaldehyde metabolism enter physiological biochemical pathways. Formaldehyde may be viewed as potentially hazardous, but its rate of formation is considered to be too low relative to the detoxification rates to raise concerns about elevation of the natural formaldehyde levels in the body.

Conclusion
The biotransformation of MTBE leads to the formation of TBA and formaldehyde which in turn are further metabolised. The toxicokinetic data do not indicate reasons for concern with regard to bioaccumulation of MTBE or its metabolites.

Acute effects
MTBE is of low acute toxicity in experimental animals by oral, dermal and inhalation routes. LD_{50} values exceed 2000 mg/kg for oral and dermal exposure, and the inhalation LC_{50} value is 85,000 mg/m^3 for 4 hours. Sub-lethal acute exposure causes local irritation at the site of contact and transient clinical signs characteristic of CNS depression. Skin contact with MTBE causes reversible moderate to severe irritation in rabbits but it is only slightly irritant to the eye. MTBE vapour at concentrations above 300 mg/m^3 causes slight and transient irritation to the respiratory system of laboratory animals. An RD_{50} of 16,600 mg/m^3 was determined in the mouse for sensory and respiratory irritation. Animal tests have revealed no potential for skin sensitisation and there are no case reports of sensitisation in humans, although contact with neat MTBE as well as gasoline containing MTBE probably has occurred in the past. This suggests that MTBE is not a skin sensitiser.

Conclusion
Transient CNS depression and mortality occur at high-doses/concentrations only. Following acute exposures to MTBE skin and respiratory irritation are regarded as the primary concern. Labelling of MTBE as „irritant“ (Xi) with the corresponding R-phrase 38 (irritating to skin) is proposed by the ECETOC Task Force.

Neurotoxicity
MTBE caused loss of consciousness in experimental animals when inhaled at concentrations of 28,800 mg/m^3. Reversible functional CNS effects were detected in a rat study at 14,400 mg/m^3 (LOAEL) using a functional observation battery and 6 hours of exposure. The NOAEL in this study was 2,880 mg/m^3. Observations suggesting transient CNS depression were also consistently found in animal studies using repeated inhalation and oral exposure. However, all effects were reversed when exposure ended and repeated exposure did not lead to lower NOAELs in comparison with the single exposure.

Conclusion
MTBE causes loss of consciousness when inhaled at exposure concentration of 28800 mg/m^3 and above. At lower exposures transient behavioural changes have been described in animal studies. The NOAEL for these reversible functional CNS effects observed after 6 hours of exposure is 2880 mg/m^3.

Repeat-dose Effects
MTBE is of low toxicity following repeated oral exposure in the rat, mouse and the monkey. Whereas the mouse and the monkey studies are of limited value, a NOAEL of 300 mg/kg was determined for the rat in an oral sub-chronic study conducted according to GLP based on increased kidney weight in both sexes. Effects were reported in females at this level, however these were not considered dose-related and were not supported by histopathology or clinical chemistry results. A study carried out in male rats only which investigated disturbances in endocrine parameters revealed increased kidney weights at below this NOAEL, however this is likely to be due to the sex-specific accumulation of MTBE known to occur in the rat kidney. A chronic oral gavage study in rats is of limited value due to reporting deficiencies, but the results do not contradict the sub-chronic NOAEL. Target organs for MTBE toxicity at higher doses have consistently been the liver and the kidney. Similar results were obtained in rats and mice after inhalation exposure. The NOAEL's for sub-chronic inhalation exposure in the rat and mouse were 2880 mg/m^3 (or 800ppm). Reversible changes in behaviour and CNS depression were also seen. Chronic inhalation studies have also demonstrated low toxicity of MTBE in mice and rats, and a NOAEL of 1440 mg/m^3 (or 400ppm) has been determined for non-neoplastic effects. Kidney effects (nephropathy) have been seen in male rats at lower concentrations, but these occur probably via a mechanism not relevant to humans. Higher concentrations also caused reversible CNS depression, but no structural damage to the nervous system. The effects are of a transient nature.

Conclusion
Principal effects identified for MTBE following repeat oral or inhalation exposure are local irritation at the site of entry, CNS effects (transient anaesthesia), kidney effects (chronic nephropathy) and liver effects (hepatocellular hypertrophy). The NOAEL for sub-chronic oral exposure is 300 mg/kg. The NOAEL for chronic inhalation exposure is 400ppm or 1440 mg/m^3. This corresponds to retained MTBE-doses in the body of 102 and 113 mg/kg/day for male and female F-344 rats, respectively, and 182 and 184 mg/kg/day for the male and female mouse, respectively.

Genotoxicity
MTBE has been tested extensively *in vitro* and *in vivo* for its genotoxic potential. It was not mutagenic in bacterial or yeast test systems, and no evidence of genotoxicity was seen for CA, gene mutation, and UDS determined in mammalian cells. A weak response in CHO cells (SCE) and a variable response in V79 cells (gene mutation) were observed. No genotoxicity was seen in the rodent cytogenetic assays, the *in vivo / in vitro* UDS assay and the sex-linked recessive lethal test in Drosophila. The weight of evidence suggests that MTBE is not genotoxic. This conclusion is supported by data on the genotoxicity of the MTBE metabolite TBA, which was negative in several *in vitro* tests and one *in vivo* assay. The other principal metabolite, formaldehyde, is mutagenic in a number of experimental systems, but toxicokinetic considerations, together with negative *in vivo* results for MTBE itself, suggest that is not a concern.

Conclusion
The available evidence does not raise concern with regard to genotoxicity of MTBE.

Carcinogenicity
The effect of high-doses of MTBE on tumour induction in experimental animals has been investigated in an oral gavage study in Sprague Dawley rats and in inhalation studies with Fischer-344 rats and CD-1 mice. In the oral study, an increase in combined lymphoma/leukaemia incidence in female rats was reported, but deficiencies in the design and initial reporting have made interpreting the significance of these results difficult. However, a re-evaluation of the material from this study in 1998 has produced a slightly clearer picture which indicates that the combining of the lymphomas and leukaemias may indeed be scientifically justifiable. This produces an apparently statistically significant increase above background levels for this strain in the high dose group, however it remains doubtful that this is a true treatment-related response as, in addition to being within the spontaneous incidence range, the opposite trend was shown to occur in males. Such a result for carcinogenicity in the cells of the immune system cannot anyway automatically be taken to infer carcinogenic potential due to the limitations of the study, it would merely suggest that such potential cannot be ruled out in this sex, strain and species.

The effect on Leydig cell tumour incidence after ingestion is regarded as specific to Sprague Dawley rats (taking into account historical control incidence within F-344 rats). The inhalation study in F-344 rats demonstrated a tumourigenic response in the male kidney at 10800 and 28800 mg/m^3 (corresponding to 384 and 1023 mg/kg/day, respectively), but a non-genotoxic mechanism unique to the male rat is probably involved. The apparent increase in the incidence of Leydig cell tumours in male Fischer-344 rats treated via inhalation was considered a background event, within the historic spontaneous range for this rat strain, whereas in Sprague Dawley rats the increased survival time confounds any observed increase. iIn addition, this tumour type is of doubtful relevance to humans.

An inhalation study with mice showed an increase in the incidence of liver adenomas in female animals at 28800 mg/m^3. This exposure concentration corresponds to a daily retained dose of 1824 mg/kg, a level in excess of the MTD and a non-genotoxic mechanism appears to be involved. This increase in the incidence of benign liver tumours at such a high dose is considered to occur by means of a mechanism not relevant to humans.

Conclusion

MTBE induces tumours in rodents at doses exceeding the MTD. Since genotoxicity appears not to be involved, the mechanism of MTBE tumour induction is considered to be secondary to toxicity in the target tissues. Further mechanistic studies are currently being conducted to clarify this. The doses necessary to demonstrate neoplastic effects are equal to or greater than doses that induce chronic non-neoplastic effects in the target tissues, liver and kidney. Therefore, protection against non-neoplastic effects will also protect from any theoretical carcinogenic effect. It is concluded by the ECETOC Task Force that MTBE does not require classification as a carcinogen according to the criteria presented in Annex VI of Directive 67/548/EEC on Dangerous Substances (EEC, 1993b). IARC has recently concluded that methyl tert-butyl ether is not classifiable as to its carcinogenicity to humans (Group 3) (IARC Vol. 73, 1999).

Reproductive, Developmental and Endocrine Effects

No effect on reproduction was observed at up to 28800 mg/m^3 in two rat studies, the NOAEL for general toxicity was 1440 mg/m^3 for the parental animals. For the rat and the rabbit, the NOAEL for developmental toxicity was greater than 9000 mg/m^3 or 28800 mg/m^3, respectively. In mice, the NOAEL for developmental and maternal toxicity was 3600 mg/m^3. At higher concentrations (14400 and 28800 mg/m^3) foetotoxicity was observed and the incidence of one malformation (cleft palate) was increased. These effects are not considered as direct effects on the foetus but secondary to concurrent maternal toxicity (reduced body weight and clinical signs of CNS effects such as hypoactivity, and ataxia).
Studies looking at the effects of MTBE on endocrine parameters showed some potential for changes to hormone levels in animals. However, these changes were mild in nature and the biological and toxicological significance remains unclear. No firm conclusions could be drawn from these data at this time.

Conclusion

MTBE is not a selective reproductive toxicant in animals and has no potential to cause adverse effects on human reproduction.

Human Experience

A large body of data is available from human experience with MTBE, including case reports of clinical use of MTBE for gallstone dissolution, studies reporting subjective complaints by garage workers and service station attendants, large population studies with sophisticated study design and controlled short-term exposure of volunteers. Whereas the early studies suggested a relationship between MTBE exposure concentration and health complaints, this has not been confirmed in subsequent studies. This absence of an association is in line with short-term experimental studies that showed no specific effects at concentrations similar to or greater than those observed in the population studies (< 3.6 - 181 mg/m^3).
Human experimental data do not indicate irritation of the respiratory tract at concentrations of 180 mg/m^3 for two hours. Exposure to 270 mg/m^3 for three hours caused mild mucous membrane irritation in some volunteers.

Objective symptoms on the CNS were not observed in experimental volunteer studies up to 270 mg/m^3. Subjective symptoms at this concentration were reported by volunteers (mainly feeling of “heaviness in the head”). At 180 mg/m^3 no symptoms were reported.

Conclusion

No consistent relationship between MTBE exposure and subjective health complaints, symptoms or objective findings has been established in population studies. Experimental volunteer studies at concentrations possibly occurring as peak exposure levels at some workplaces demonstrated a NOAEL of 180 mg/m^3. Mild subjective symptoms and slight irritation of mucous membranes were reported at 270 mg/m^3.

Identification of relevant end points and NOAELs

Table 4-32 summarises the conclusions with regard to MTBE-related effects observed after short-term and long-term exposure of human and experimental animals. Irritation observed after short-term exposure in humans, as well as liver and kidney toxicity observed after long-term exposure in experimental animals, are regarded as critical effects for the risk characterisation of MTBE. Mild respiratory irritation occurred at a concentration 270 mg/m^3 for three hours in human volunteers, while a concentration of 180 mg/m^3 for two hours did not cause such effects. The lowest NOAEL for liver and kidney effects after chronic inhalation exposure was 102 mg/kg/day (retained dose).

Table 4-32: Principal adverse effects of MTBE and NOAELs

End point	Species	Route	Exposure Time	Principal Effects	NOAEL	Remarks	Reference
acute effects	man	inhalation	2 hours (during light physical exercise)	mucous membrane irritation	180 mg/m^3	subjective symptoms (like slight irritation and heaviness in the head) were reported at 270 mg/m^3 (3 hrs)	Johanson *et al*, 1995 Riihimäki *et al*, 1996
subchronic toxicity	rat	inhalation	90 days	liver and kidney toxicity (males)	2,880 mg/m^3 (800ppm)	equivalent to 228 mg/kg bw/day (males)	Dodd and Kintigh, 1989
chronic toxicity and neoplastic effects	rat	inhalation	105 weeks	liver and kidney toxicity, kidney tumours (males)	1,440 mg/m^3 (400ppm)	equivalent to 102 mg/kg bw/day (males)	Chun *et al*, 1992
	mouse	inhalation	18 months	liver tumours (females)	10,800 mg/m^3	equivalent to 669 mg/kg bw/day (females)	Burleigh-Flayer *et al*, 1992
neurotoxicity	rat	inhalation	6 hours	functional CNS effects	2,880 mg/m^3	LOAEL was 14,400 mg/m^3; effects were reversible	Gill, 1989
effects on fertility	rat	inhalation	two generations	no treatment related effects	> 28,800 mg/m^3	for parental toxicity a NOAEL of 1,440 mg/m^3 was determined	Myhr *et al*, 1991
developmental toxicity	mouse	inhalation	gestation days 6 to 15	no direct effect on the foetus	3,600 mg/m^3	higher concentrations caused maternal toxicity and secondary developmental toxicity	Tyl and Neeper-Bradley, 1989

4.1.3.1 Workers

MTBE production

Production is associated with relatively low exposures (<10 mg/m^3 over 8 h), while loading operations may result in higher exposures (20 mg/m^3, with peak exposure around 200 mg/m^3). Assuming an inhalation volume of 10 m^3 per 8-hour shift and a relative respiratory uptake of 40%, exposure to a concentration of 10 mg/m^3 would result in a retained amount of 40 mg MTBE per day corresponding to a dose of 0.57 mg/kg for a 70 kg adult. The lowest NOAEL from chronic animal inhalation studies is 102 mg/kg/day. Comparison of these two doses leads to an approximate 300 fold margin of safety for workers involved in production. For loading operations, a 180 fold margin of safety is apparent. Comparison of the maximum exposure values of about 200 mg/m^3 with the concentration, which caused slight mucous membrane irritation in some volunteers (270 mg/m^3), does not indicate concern.

Blending, distribution and handling of gasolines containing MTBE

Mean short-term exposure measurements for loading and delivery of gasoline containing 10-15% MTBE were between 13-91 mg/m^3 with a maximum of 226 mg/m^3. These values were well in excess of the measured values for blending operations which indicated maximal worker exposures of up to 9.5 mg/m^3. Since most fuels in Europe only contain MTBE at around 2% (as an octane enhancer), these findings were considered by the Task Force to be a 'worst case' situation .In general, these loading and delivery operations lasted around 30 minutes, with mean short-term exposure below 100 mg/m^3. Assuming a ventilation rate of 1.25 m^3/h and a relative respiratory uptake of 40%, exposure to such a concentration for 30 min would result in a retained amount of 25 mg MTBE per exposure period, corresponding to a dose of 0.36 mg/kg. Assuming a worst case of 4 exposures per day, this would lead to a daily dose of 1.44 mg/kg. The lowest NOAEL from chronic animal inhalation studies is 102 mg/kg/day. Comparison of these two doses leads to an approximate 70-fold margin of safety for workers involved in loading and delivery of gasoline containing high percentages of MTBE. Comparison of the maximum exposure values of about 226 mg/m^3 with the concentration, which caused slight mucous membrane irritation in some volunteers (270 mg/m^3), does not indicate concern.

Service-station attendants and garage workers

Monitoring data from the US show a highest mean exposure to MTBE of approximately 3.5 mg/m^3, with the highest individual value of 7.56 mg/m^3. Assuming a ventilation volume of 10 m^3 per 8-hour shift and a relative respiratory uptake of 40%, an exposure concentration of 3.5 mg/m^3 would result in a retained amount of 14 mg, corresponding to a dose of 0.2 mg/kg per day for a 70-kg adult. The lowest NOAEL from chronic animal inhalation studies is 102 mg/kg/day. Comparison of these two doses leads to an approximate 800 fold margin of safety for workers involved in loading and delivery of gasoline containing high percentages of MTBE. The highest observed exposure value would give an approximate 250 fold margin of safety. For service-station attendants and garage workers irritation due to MTBE is not a concern.

Recommended Occupational Exposure Limit

An occupational exposure limit of 90 mg/m^3 or 25 ppm (8-h TWA) is proposed for workers handling MTBE. This concentration corresponds to a daily retained MTBE dose of about 5.1 mg/kg (on the basis of a ventilation volume of 10 m^3/8-h shift and a relative respiratory uptake of 40%) and provides a margin of safety of 20 when compared with the lowest NOAEL determined in chronic animal inhalation experiments. Respiratory irritation is regarded as the critical effect for higher short-term exposures. In humans, at a concentration of 180 mg/m^3 for 2 hours no effects were observed while at 270 mg/m^3 for three hours only slight irritating effects on the mucous membranes were reported in some volunteers. Therefore, a limit of three times the TWA (270 mg/m^3 or 75 ppm) is considered to be an appropriate short-term, peak exposure limit (15-min STEL).

Result statement

For the workers population exposed to MTBE it is considered that result statement ii) applies.

4.1.3.2 Consumers

On the basis of the limited information available mean short-term exposures during car refuelling are calculated as 6 mg/m^3 for about 1 minute. The gasoline used in the Finnish study that provided these data had a MTBE content of 11% w/w, whereas in other European areas a lower MTBE content gasoline is used. Therefore maximum mean short-term exposures of about 10 mg/m^3 and a refuelling duration of about 5 minutes appear a realistic worst case scenario. Such exposure would lead to a retained amount of about 0.42 mg using an inhalation rate of 1.25 m/h and a retention of 40% for an adult human being (70 kg). This results in a dose of about 0.006 mg/kg. Comparison with the NOAEL of 102 mg/kg obtained in chronic inhalation studies indicate a margin of safety of approx. 17000 for consumers in this situation.

Result statement

For the consumer population exposed to MTBE it is considered that result statement ii) applies.

4.1.3.3 Man exposed indirectly via the environment

The risk characterisation for indirect exposure is performed by calculating the margin of safety (MOS), i.e. the ratio between the total daily intake and the relevant exposure parameter, which is the (sub)chronic oral N(L)OAEL. It is assumed here that man is exposed throughout his or her lifetime. A subchronic N(L)OAEL is only used if no chronic value is available, and such cases need extra attention in the evaluation of the MOS. MOSs have been calculated for MTBE using EUSES data for the following exposure scenarios: Local - Production (Use pattern 1), Formulation (Use pattern 1), Processing (Use patterns 1, 2 and 3) and Regional. Additionally, the air concentration to which man is estimated to be exposed can be compared to the subchronic inhalatory LOAEL, if available. This inhalatory value is not estimated from oral data.
A margin of safety (MOS) of greater than one implies that the level of exposure is lower than the no effect level and hence that there is no inherent risk resulting from that level of exposure for that substance.

Result statement

For the human population exposed to MTBE via the environment it is considered that result statement ii) applies.

Table 4-33 : Margin of Safety (MOS) result table for MTBE used as a fuel additive, as an isobutylene production intermediate and as a solvent with estimated emission factors

Scenario	MOS	
	Total (all routes/media)	**Air**
Local		
Production – Use pattern 1	3.33E+04	855
Formulation – Use pattern 2	2.4E+04	6.08E+03
Processing – Use pattern 1	1.38E+04	5.73E+03
Processing – Use pattern 2	2.35E+03	797
Processing – Use pattern 3	6.64E+05	1.33E+05
Regional	7.88E+05	1.44E+05

4.2 HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES)

4.2.1 Exposure assessment

4.2.1.1 Occupational exposure

Not discussed here.

4.2.1.2 Consumer exposure

Not discussed here.

4.2.1.3 Indirect exposure via the environment

Indirect exposure via the environment and the influence on this of key physicochemical properties is dealt with in detail in other sections of the report. Assessment of the indirect exposure via the environment to other physicochemical properties such as explosivity, flammability and oxidising potential is not relevant for this particular substance and its modes of use.

4.2.2 EFFECTS ASSESSMENT: HAZARD IDENTIFICATION AND DOSE (CONCENTRATION) RESPONSE (EFFECT) ASSESSMENT

4.2.2.l Explosivity

MTBE can form explosive mixtures with air. Auto-flammability is recorded as occurring at 375°C.

4.2.2.2 Flammability

MTBE is highly flammable and combustible, with the following flammability limits reported in the HEDSET:

Lower: 1.5% vol. in air
Upper: 8.5% vol. in air.

4.2.2.3 Oxidising potential

No data.

4.2.3 RISK CHARACTERISATION

4.2.3.1 Workers

For the worker population exposed to MTBE via the environment it is considered that result statement ii) applies.

4.2.3.2 Consumers

For the consumer population exposed to MTBE it is considered that result statement ii) applies.

4.2.3.3 Man exposed indirectly via the environment

For the human population exposed to MTBE via the environment it is considered that result statement ii) applies.

5 RESULTS / CONCLUSIONS

Direct exposure to man

Irritation observed after short-term exposure in humans as well as liver and kidney toxicity observed after long-term exposure in experimental animals are considered to be the critical effects for the health risk characterisation of MTBE. The basis for the risk characterisation is a comparison of three different doses / concentrations for these effects with occupational and consumer exposure data. This produced margins of safety (MOSs) between 180 to 300 fold for workers involved in MTBE production, about 70 fold for workers handling gasolines containing MTBE, and between 250 to 800 fold for service station attendants and garage workers. A 17000 fold margin of safety was calculated for consumer exposure during car refuelling. Compliance by workers with the short- and long-term occupational exposure limits for MTBE in the ECETOC report of 270 mg/m3 (75ppm) and 90 mg/m3 (25ppm) respectively is considered likely to be protective regarding the above effects.
The risk characterisation produced here for occupational and consumer exposure to MTBE does not indicate concern for human health.

Indirect exposure to man / exposure to the environment

An environmental risk assessment for all uses of MTBE (as a fuel oxygenate, as a production intermediate for isobutylene and as a speciality solvent) was carried out using the European Union System for the Evaluation of Substances (EUSES). Where data was available, realistic worst case estimates of emission factors were used

rather than the TGD default values. The assessment produced acceptable (<1.0) risk characterisation ratios (RCRs) and acceptable (>1.0) margin of safety (MOS) values for all stages of the life-cycle, except for three situations. These were the local sediment compartment for Production for use pattern 1 and both the local water and sediment compartments for use pattern 2. The recommended action was to consider carrying out sediment toxicity test and to implement a statistically designed sampling and analysis programme to measure concentrations of MTBE in wastewaters from sites using MTBE for isobutylene synthesis.
Overall the results of the risk assessment, using the factors described in this report, indicates that the environmental risk of using MTBE as a fuel additive, process intermediate or a solvent is low.

CONCLUSION

It is considered that for all human populations exposed to MTBE via all exposure scenarios, result ii) applies : on the basis of all available information, at present no further information/testing on the substance is needed and at present no further risk reduction measures (beyond those being applied already), are necessary. However, for environmental compartments exposed to MTBE via wastewater discharges from production (use pattern 1) and processing (use pattern 2), result i) applies : there is a need for further information and/or testing.

6 DATA SOURCES

This report contains data collated from two previously published reports (ECETOC Technical Report No. 72, WRc plc Environmental Risk Assessment Of MTBE Using EUSES for the EFOA. (for full details see References section) and from the data in the HEDSET (ARCO Chemical Company, July 1997) for this compound. Where data are taken from alternative sources, the appropriate reference is provided. Such alternative data sources include the Internet, databases such as ACQUIRE and the open scientific literature.

INFORMATION ON EUSES

EUSES is a software package which has been produced by the EU to assist in the risk assessment of new and existing chemicals required under EU Directive 92/32/EC and EC Council Regulation 793/93. Essentially, EUSES is a software implementation of the Technical Guidance Document (TGD) in support of the Commission Directive and Regulation on risk assessment of new and existing chemicals. EUSES facilitates the quantitative assessment of the risks posed by chemicals to man and the environment. The risk assessment is carried out in a stepwise procedure starting with data input and estimation and further involving the estimation of emissions, the prediction of environmental distribution the calculation of human and environmental exposure, the derivation of no-effect levels and risk characterisation. The exposure assessment in EUSES covers the whole life cycle of substances (production, formulation, processing, use and recovery) as well as their fate in all environmental compartments and the end-point is a quantitative comparison for the substance of the results of the effects and the exposure assessments. The resulting risk characterisation ratios (RCRs: PEC/PNEC ratios) for environmental compartments and margins of safety (MOS: PNEC/PEC) for indirect effects on humans can be regarded as indicators for the likelihood of adverse effects occurring.

Table 6-1 : Human populations and ecological systems and populations assessed in EUSES:

Human populations	Ecological systems and populations
• Workers • Consumers • Man exposed via the environment	• Micro-organisms in sewage treatment • Aquatic ecosystem • Terrestrial ecosystem • Sediment ecosystem • Top predators