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# PRELIMINARY RISK ASSESSMENT OF STYRENE PRODUCTION

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ABSTRACT: Styrene (phenyl ethane; CAS: 100-42-5) is widely used in the production of plastics, synthetic rubber, polyester resins. Styrene, as one of the substantial feedstock for petrochemical industry, has become of high interest in Kazakhstan. Thus, according to the national petroleum companies' plan, a styrene production plant project will be in operation by 2017 in Aktau city, Kazakhstan.

Styrene is also recognized as an environmental pollutant. Thus, apart from the industrial use it appears in the small amounts in, e.g. various foods, tobacco smoke and engine exhausts.

Styrene emissions may have significant impact on environmental and human health. Styrene is moderately toxic to aquatic organisms, however, readily biodegradable under aerobic conditions. In relation to human health styrene is hematotoxic and it causes skin, eye and respiratory tract irritation. Styrene should be regarded as a potential carcinogen and mutagen.

The present paper presents a simple preliminary risk assessment approach illustrated by the planned setting up a styrene production plant in Kazakhstan. The objectives being to identify the potential risks prior to the construction phase in order to prevent the negative aspects linked to styrene. The assessment has been compiled using the DPSIR principle as framework and applying freely available assessment tools such as QSAR/QSTR models, Material Safety Data Sheets and rule-based screening tools in combination to available information from the literature.

A simple assessment based on the BenchMark Dose and Margin Of Exposure methodologies (MOE) is presented, suggesting that styrene emissions in all cases must be taken seriously.

The methodology applied in the present paper can immediately be transferred to other potentially hazardous compounds.

Keywords: Styrene, Risk assessment, Production, Environment, Human health.

## 1. INTRODUCTION

Styrene (phenyl ethane; CAS: 100-42-5) is one of the most essential plastic monomers worldwide. It is primary used as precursor for polystyrene. Styrene was commercially first produced in the 1930 s and played an important role during World War 2 in the production of synthetic rubber. After the war, much of the use of styrene shifted to the manufacture of commercial polystyrene products, e.g. automobile parts, electronic components, boats, recreational vehicles, and synthetic rubbers. Today styrene based products are omnipresent worldwide (Hempstead, 2005).

Petroleum chemistry plays a significant role in Kazakhstan's economy. The worldwide apparently non-terminating demand for petrochemical products has been growing annually. Thus, producers are apparently unable to provide sufficiently amounts of styrene. As a result investors are focusing their attention on this sector. Apparently one the most attractive field for the Kazakhstan industrial economy appears to be styrene monomer production. Hence, the Aktau Plastics Plant of polystyrene production has an increasing demand for raw material that beneficially should be supplied through a local

production. Scrutinizing the world's demand of petrochemical products shows that setting up local production facilities to produce ethylene, polyethylene, polypropylene, styrene, polystyrene, ethylene glycol and benzene apparently would be beneficial for Kazakhstan (KIBM, 2006).

As far as the Kazakhstan economy is concerned, there are several positive options, which can be exemplified through free supplying feedstock to the current and future refining plants, as a result a priori may lead to significant development in the area of petrochemistry.

The objective with the present study is to carry out a preliminary risk assessment of the planned styrene production, which is foreseen to be in operation in 2017 by KazMunaiGas (KIBM, 2006). Thus, we have an opportunity to assess and predict the possible risks that Kazakhstan might be confronted with in this context as possible accidental and/or deliberate emissions of styrene to the environment may have adverse effects both on the environmental and human health. In the present paper we focus on the possible adverse impacts of styrene on the environment and human health based on literature studies as well as QSAR/QSTR studies. The assessment has been carried out applying the DPSIR framework (Kristensen, 2004).

## 2. METHODS

The DPSIR (Driving forces, Pressures, State, Impacts, Responses) framework (Kristensen, 2004) takes into account a chain of past and present situations as well as suggests future activities as responses aiming at improving the environmental health.

### 2.1 Driving Forces

The driving forces are centered on economic sectors and human activities, i.e. activities in the society that directly or indirectly are causing the pressures on the environment. Roughly speaking the driving forces can be classified as those creating the nuisance and those consuming resources. Thus, in broad terms driving forces comprise population, economy, land use and societal development. More specific examples of driving forces comprise manufacturing and Industry, energy production, transport systems, agricultural activities, fisheries, households and consumers and waste treatment, the list by no means being exhaustive. In sum driving forces can be regarded as 'needs' for individuals, industry or society.

### 2.2 Pressures

The impacts (pressures) on the environment develop from the human activities that are associated with meeting the above mentioned 'needs' (driving forces). Thus, the pressures are results of production or consumption processes, such as non-sustainable use of resources, changes in land use, and direct and indirect emissions of chemicals, waste, etc. to air, water and soil.

### 2.3 State

The state refers to the environmental and human health as a result of the pressures. Hence, the state comprises a combination the physical, chemical and biological quality of the various environmental compartments, i.e. soil, water and air, as well as their mutual interplay with respect to, e.g. the biodiversity, vegetation water and soil organisms within a specific ecosystem, a specific type of landscape, a given population, etc.

### 2.4 Impacts

The impacts refer to environmental and economic factors. Thus, the possible changes in the physical, chemical or biological states may unambiguously cause impacts on the environmental and human health, e.g. as a result of increasing concentrations of hazardous chemicals in the environment and eventually on both the economic and social performance of society.

Ultimately the impacts focus on changes in the human welfare comprising both physical and mental health as a result in changes in the quality, e.g. state, of the environment. However, also the possible changes in the environmental health due to changes in the physical, chemical and/or biological state may be covered here.

### 2.5 Responses

The responses comprise a priori the reactions by authorities, regulators or society in general to the changes induced through the other element in the DPSIR chain. Thus, responses could comprise both passive and active measures. Hence a passive measure, relating to driving forces could be initiatives, to change people's transport pattern from private cars to public transportation by making zones where private cars are not allowed, whereas an active measure would be an increase of taxes on gasoline to motivate people to use alternative modes of transportation.

Responses related to pressures would be various regulations aiming at a reduction of the emissions of hazardous chemicals to the environment, whereas responses related to state would comprise, e.g. cleaning up or remediation projects of contaminated land.

It is noted, that basically all responses are caused by the impact element. Impacts are results of possible changes in driving forces, pressures and/or state. Obviously, if no changes in these element and thus no chances in impacts, imposing responses as the above mentioned, it cannot be argued. In Fig. 1 the complete DPSIR framework is visualized.

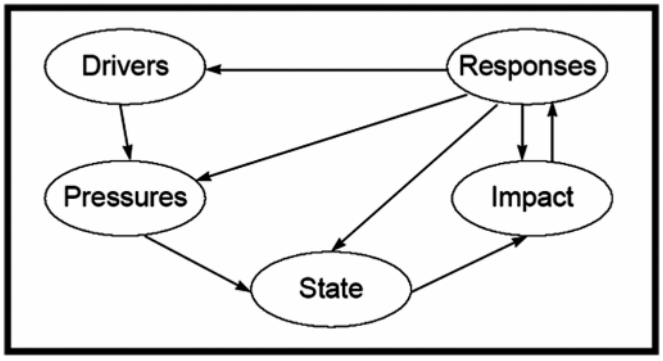


Fig. 1: The Interrelation between the Single Elements in the DPSIR Framework (Adopted from Kristensen, 2004)

## 2.6 Physico-chemical Data

Physico-chemical end-points are generated through QSAR modelling, the EPI Suite being the primary tool (EPA, 2008a) and compared to experimental data, when available. The single parameters were calculated applying the various submodules of the EPI Suite: WSKOW (water solubility, log SW), KOWWIN (octanol-water partitioning, logKOW), MPBPWIN (vapour pressure, logVP), HENRY (Henry's Law constants, logHLC), AEROWIN (sorption to atmospheric particulates) and PCKOCWIN (Sorption to organic carbon, logKOC). The log KOW values generated in this way are subsequently used to generate bioconcentration factors (log BCF) calculated by the submodule BCF program. Substances exhibiting log BCF values of > 3.0, but < 3.70 are assigned a medium bioconcentration potential whereas substances with log BCF > 3.70 were assigned a high bioconcentration potential. (EPA, 1999). Substances with log BCF < 3.0 were regarded as non-bioaccumulating.

## 2.7 Environmental Persistence

Through the BioWin and BioHCWin modules (EPA, 2008a) the persistence of styrene in the environment was predicted. The submodules BDP1 and 2 indicate if the compound is readily or non-readily biodegradable, whereas the submodule BDP3 provides estimates of the environmental biodegradation rate by calculating the degradation probabilities. The lower the probability the higher the persistence. Eventually BDP3 returns the biodegradation potential as hours, hours to days, days, days to weeks, weeks, weeks to months and months, respectively, depending on the approximate amount of time needed for a "complete" biodegradation (EPA, 2008a; Walker and Carlsen, 2002).

| BDP3 | Predicted half-lives (days) |
|---|---|
| Hours | 0.17 |
| Hours to Days | 1.25 |
| Days | 2.33 |
| Days to Weeks | 8.67 |
| Weeks | 15 |
| Weeks to Months | 37.5 |
| Months | 60 |
| Recalcitrant | 180 |

Substances with half lives > 180 days are assigned high persistence potential, the corresponding BDP3 value being < 1.75, whereas substances a half-life in the predominant compartment of ≥ 60 and ≤ 180 days are assigned medium persistence potential, the corresponding BDP3 value being > 1.75 and < 2.0 (Walker and Carlsen, 2002).

The fate in the aquatic media was, in addition to the biodegradation estimated as the potential for volatilization from water. In the present study volatilization from rivers (water depth 1m, wind velocity 5 m/s and current velocity 1 m/s) and from lakes (water depth 1 m, wind velocity 0.5 m/s and current velocity 0.05 m/s) was calculated using the WVOLWin module in EPI Suite (EPA, 2008a). Finally the Mackay's Level 3 Fugacity Model was used to estimate the fate of emitted styrene from the production plant (EPA, 2008a).

## 2.8 HARVARD CENTER OF RISK ANALYSIS

Material from the Harvard Center of Risk Analysis (HCRA) (Cohen, 2002) has been included as an integrated part of the present study. A panel of independent experts evaluated the risk to workers

and the public from styrene exposure. Styrene impact on mice and rat was tested. In addition extensive studies of occupationally exposed populations were conducted to elucidate the possible carcinogenicity of styrene to humans. Additional studies assessed the exposure studying the concentrations of styrene in air and in blood.

### 2.9 Material Safety Data Sheets

The Material Safety Data Sheet for styrene (MSDS) was included in the study as part of developing a possible prevention strategy.

As a supplement to the data available from HCRA and the MSDS we applied QSAR/QSTR methodology to calculate physic-chemical parameters as well as to predict possible environmental and human toxicological characteristics of styrene.

### 2.10 Environmental Toxicity

Environmental toxicities of styrene were obtained by (EPA, 1994; 2009) that calculates the toxicity of styrene discharged into water. Both acute (short-term) toxicities and chronic (long-term or delayed) toxicities are calculated by ECOSAR, the calculations being based on the octanol-water partitioning (logKOW). ECOSAR can run independently or as an integrated part of the EPI Suite.

ECOSAR returns the acute as well as chronic toxicities to fish (both fresh and saltwater), water fleas (daphnids), and green algae as well as to earthworms. The acute toxicities are calculated as LC50 values.

The absorption, distribution, metabolism and excretion features of styrene were addressed by ADME Boxes (Pharma Algorithms). The toxicological effects were derived by ToxBoxes (Pharma Algorithms) and by PASS (PASS1).

### 2.11 Absorption, Distribution, Metabolism and Excretion (ADME)

Predictions for the absorption, distribution, metabolism and excretion (ADME) and Toxicology of styrene were obtained using the freely and commercially available in silico expert systems, i.e. the web version of the ADME Boxes software (Pharma Algorithms) based on ADME Boxes ver. 3.5. ADME Boxes is modulized software that allows calculation of selected physico-chemical data, oral bioavailability (human), human intestinal absorption, transport, distribution including volume of distribution and plasma bound fraction based on the chemical structure. The software modules are based on exacting data analyses and expert models for calculating the vital properties.

### 2.12 ToxBoxes

Acute toxicity of styrene towards mouse and rat as well as the probability of adverse organ specific health effects affecting the blood, the cardiovascular- and gastrointestinal systems, the kidneys, the liver and the lungs, respectively and a positive response in an Ames test is derived using the web version of the ToxBoxes software (Pharma Algorithms) based on ToxBoxes ver. 2.0. ToxBoxes is a modulized software that allows calculation of toxic effects of molecules solely from the chemical structure (SMILES notation) in combination with expertise in organic chemistry and toxicology.

### 2.13 Prediction of Activity Spectra for Substances (PASS)

The computer program PASS (Prediction of Activity Spectra for Substances) developed by the Academy of Medical Sciences, Moscow, predicts the biological activity for a compound on the basis of its structural formula (PASS1).

In the present study the PASS internet version has been applied that allows the prediction of 3678 pharmacological effects as well as mechanisms of action (PASS2). The present study focuses on carcinogenicity, mutagenicity, teratogenicity and embryotoxicity. In the case of carcinogenicity the highest value obtained (male/female mice, male/female rats) were applied as a conservative measure.

## 3. RESULTS AND DISCUSSION

The DPSIR model (Kristensen, 2004) as framework for an integrated assessment, in the present case of the planned production of styrene constitutes an advantageous tool to elucidate the causality of the links between the single elements as illustrated by the arrows in Fig. 1. It must be emphasized that the present study focus on the external environment and does not aim at a closer discussion of the working environment, which obviously has to be taken care of as an integrated part of the construction, and later production phase.

### 3.1 Driving Forces

As made obvious in the introduction major economic interests are in plays when discussing the

planned production of styrene in Kazakhstan, these interests constituting the driving forces.

Obviously the driving forces are the most fundamental in the assessment as these activities are the actual source of the environmental, and thus eventually human health problems and a possible removal of these activities will unambiguously diminish or, in the long run possible eliminate the problems. However, a deeper discussion on the driving forces is outside the scope of the present paper.

### 3.2 Pressures

In the case of the planned production of styrene the pressure to the surrounding environment appears to be almost exclusively of chemical nature, i.e. deliberately or accidental emissions of styrene from the plant to the environment. Hence, in order to diminish the pressure due to styrene emissions, it appears evident that threshold values have to be set up for the possible deliberate emission (cf. Section 3.5).

### 3.3 State

As the production of styrene for the time being is only on the drawing board, it is for now not possible to elucidate the state of the environment further in this connection. However, it is strongly emphasized, that before starting the production a monitoring program should be set up and possible background concentrations must be determined (cf. the discussion in Section 3.5).

### 3.4 Impacts

The possible impact of styrene emitted from the planned production plant as well as from the plants for further processing of styrene, e.g. polystyrene production, towards both the environment and to the surrounding population has to be evaluated in order eventually to assess the potential risk associated with the production.

#### 3.4.1 Physico-chemical Data

Styrene is a viscous, highly flammable liquid (Class 3 according to the Materials Safety Data Sheet (MSDS)) used worldwide in the production of polymers, which are incorporated into products such as rubber, plastic, insulation, fiberglass, pipes, automobile parts, food containers, and carpet backing, etc. The physico-chemical characteristics of styrene are well documented (cf. Table 1). For comparison also QSAR generated data are shown. The correspondence between the experimentally and theoretically data is striking.

Table 1
Physico Chemical Data for Styrene (EPA, 2008a)

| Endpoint | Experimental value | EPI Suite derived value |
|---|---|---|
| Water solubility (log $C_W$) | 2.49 mg/L | 2.54 mg/L |
| Octanol-Water partitioning (log $K_{OW}$) | 2.95 | 2.90 |
| Octanol-Air partitioning (log $K_{OA}$) | – | 3.90 |
| Water-Organic carbon partitioning (log $K_{OC}$) | 2.96 | 2.65 |
| Henry's Law Constant (HLC) | 279 Pa-$m^3$/mole | 285 Pa-$m^3$/mole [a] |
| Vapor pressure (VP) | 853 Pa | 887 Pa |
| Bioconcentration Factor (log BCF) | 1.13 | 1.61 |

[a] group estimate.

#### 3.4.2 Environmental Toxicities

In Table 2 the calculated environmental toxicities towards a variety of aquatic organisms are depicted as derived applying the ECOSAR software (EPA, 1994; 2009).

Table 2
ECOSAR (EPA, 1994; 2009) Derived Ecotoxicity Data for Styrene (Class: Neutral Organics)

| Species | Test time | Endpoint | Value (mg/L) |
|---|---|---|---|
| Fish | 96 hrs | LC50 | 13.09 |
| Fish | 14 days | LC50 | 13.43 |
| Fish | 30 days | Chronic | 1.45 |
| Fish (salt water) | 96 hrs | LC50 | 17.01 |
| Fish (salt water) | – | Chronic | 3.19 |
| Daphnid | 48 hrs | LC50 | 8.43 |
| Daphnid | – | Chronic | 1.13 |
| Green Algae | 96 hrs | EC50 | 5.90 |
| Green Algae | – | Chronic | 2.62 |
| Mysid Shrimp | 96 hrs | LC50 | 6.90 |
| Mysid Shrimp (salt water) | – | Chronic | 0.46 |
| Earthworm | 14 days | LC50 | 146.24 |

### 3.4.3 PBT Characteristics

In connection to an environmental risk assessment the PBT (Persistence, Bioacumulation, Toxicity) characteristics are of importance (EC, 2006). However, from the above tables it is immediate clear that styrene should not be classified as a PBT compounds.

The possible persistence in the environment identified applying the BioWin and AOP modules of the EPI Suite (EPA, 2008a). Based on these calculations, it can be concluded, that styrene is fairly rapidly biodegraded (apparently within a week) under aerobic conditions. Applying the BioHCWin module the half life was calculated to be 3.9 days. Under anaerobic conditions styrene apparently is only slowly degraded. The overall conclusion of the BioWin calculations were the styrene should not be regarded as readily biodegradable (EPA, 2008a).

A priori strong sorption to organic carbon may be expected to increase the environmental persistence. However, the log $K_{OC}$ value of 2.96 (Table 1) does not justify the assumption of an increased persistence due to sorption.

On the other hand, the moderate vapor pressure (Table 1) suggests that styrene may to a certain extent evaporate from dry polluted soils. Likewise the relative low solubility combined with the moderate Henry's Law Constant (Table 1) suggest only a minor evaporation from water and thus from moist soils as well, the calculated air-water partitioning coefficient, log $K_{AW}$, being calculated to –0.95 (EPA, 2008a).

In air the predominant degradation pathway apparently is the reaction with hydroxyl radicals. The rate constant was calculated to be $28.1 \times 10^{-12}$ $cm^3$/day (experimental value: 58x10-12 cm3/day) the corresponding half life being estimated to be 4.56 hrs.

The bioconcentration factor, log BCF, equals 1.6 indicates that the compound is not bioaccumulating to any significant extent and only moderate toxicities to aquatic organisms are predicted, apart from the case of Mysid Shrimp (SW) where a chronic value of 0.46 mg/L was predicted (Table 2).

### 3.4.4 Compartmental Distribution

The compartmental distribution of styrene, deliberately or accidentally emitted to the environment was estimated using the Mackay Level 3 fugacity model (MacKay, 2001) that is an integrated part of the EPI Suite (EPA, 2008a). In the case of a styrene production plant the most probable release scenarios will be release to the air. In Table 3 the calculated distributions are given following a 1000 kg/hr emission of styrene to the air. The overall persistence time of styrene was calculated to be 4.6 hrs. This figure results from a 4.82 hrs persistence due to reaction (95.5%) and 102 hrs due to advection (4.52%), respectively.

Table 3
Compartmental Distribution and Removal According to the MacKay Level 3 Fugacity Model for Emissions to Air, Soil and Water of 1000, 0 and 0 kg/hr, Respectively (EPA, 2008a)

| Compartment | Compartmental distribution (%) | Removal by reaction (kg/hr) | Removal by advection (kg/hr) |
|---|---|---|---|
| Air | 98.3 | 955 | 45.2 |
| Water | 0.773 | 0.0684 | 0.0356 |
| Soil | 0.992 | 0.0408 | 0 |
| Sediment | 0.138 | 0.00014 | $1.27 \times 10^{-5}$ |

'Based on the results given in Table 3 it can be concluded that, not surprisingly taken the emission pathway as well the relative high vapor pressure into account that the main part of the styrene will be found in the air. Further it is evident that the above discussed reaction mechanism, e.g. the degradation in air, is the main process for removal of styrene from the air compartment as only minor amounts are seen to be removed by advection.

It is, however, also clear that even though the overall residence time is rather low, 4.6 hrs, it is crucial to limit emissions of styrene, deliberate and/or accidental as even within this short time period residential areas in the near vicinity may be reached by the plume, cf. the discussion about margin of exposure values (MOE) below.

### 3.4.5 Environmental Risk Assessment

Obviously, the yearly production of styrene plays an important role in assessing the actual risk of the production scenario. To carry out a complete environmental risk assessment, which may be done applying the EUSES concept (RIVM, 2004) is a major task. Thus, EUSES requires more than 450 input parameters, more than 950 connection between input parameters and more than 130 default values, selection of one 4 main categories, one of 15 industry

categories and one of 55 use categories (Berding et al., 1999). However, in their paper from 2005 Verdonck et. al. (2005) reported a simple rule-based screening tool derived from EUSES based on biodegradability, log $K_{OW}$, and log VP as the key parameters in combination with the release scenario, tonnage and ecotoxicity expressed as the Predicted No Effect Concentration (PNEC) value. The maximum Risk Characterization Ratio, $RCR_{max}$, was eventually calculated based on the formula.

$$RCR_{max,tonnage,PNEC} = \frac{RCR_{max,lookuptable} \cdot 1\mu g/L}{1 tonne/year} \cdot \frac{tonnage\ (tonne/year)}{PNEC\ (\mu g/L)}$$

where $RCR_{max,\ tonnage,\ PNEC}$ is the maximum RCR value for the given production volume, L, and the actual PNEC value of the substance under investigation. $RCR_{max,\ lookuptable}$ is retrieved from a so-called lookup table that has been generated statistically. For details the reader is referred to the paper by Verdonck et al. (2005).

In the case of styrene the log $K_{OW}$ and the log VP values are found to be 2.95 and 2.93, respectively and the compounds is found to be readily biodegradable. Based on the calculated ecotoxicities (Table 2) it appears reasonable to assign a conservative PNEC value for styrene to 1 µg/L, corresponding to the application of an assessment factor of 1000 (Zeeman and Gilford, 1993). Hence, from the lookup table (Verdonck et al., 2005) we derive a $RCR_{max,\ lookuptable}$ to 2.12 using the 95th percentile. Consequently we get $RCR_{max,\ tonnage,\ PNEC} = 2.12 \times L$, i.e. if the yearly production of styrene will be, e.g. 100,000 tonnes the maximum risk characterization coefficient, $RCR_{max,\ tonnage,\ PNEC}$, will be 2,120,000 strongly suggesting that a more thorough environmental risk assessment is needed.

### 3.4.6 Human Health Impact

Turning to the possible impact by styrene on the human health we unambiguously acknowledge the comprehensive literature available on styrene. However, the present paper is not an attempt to review all available material but merely to look at available summaries and recommendations and to further qualify the discussion based on appropriate QSAR/QSTR generated data. Hence, in the present paper we take our starting point in the work carried out by the Harvard Center of Risk Analysis (HCRA) (Cohen, 2002) and what is summarized in the Material Safety Data Sheet (MSDS) for styrene (MSDS) as well in the ASTDR toxicological profile of styrene (ASTDR).

Airborne styrene exposure originates from industrial activities and motor vehicle exhaust, with typical ambient concentrations reaching around 1 part per billion (ppb). For smokers, the dominant source of inhaled styrene is through smoking cigarettes, which may increase the average exposures for these individuals up to 6 ppb. Further, the panel estimated (Cohen, 2002) that a conservative evaluation lead to the conclusion that individuals living close to large styrene manufacturing facilities could be exposed to lifetime average ambient concentrations exceeding 200 ppb.

Dietary exposure may originate from naturally occurring styrene in foods such as strawberries, beef, and spices (Cohen, 2002) and amounts typically to 10ppm (Gold, 1999).

Over the years the occupational exposure to styrene has steadily declined due to improved industrial hygiene and more stringent regulations, but it remains substantially higher than exposure to the general public (Cohen, 2002). As examples can be mentioned the fiberglass-reinforced plastics segment of the styrene industry, where exposures are highest. Here measurements indicate that airborne concentrations today are less than 20 parts per million (ppm) (Cohen, 2002). In other styrene industry segments, exposures are estimated to be as low as 5 ppm or less (Cohen, 2002).

In their study the HCRA summarized data for 3 styrene production plants (Vodicka, 2004). comprising a styrene-exposed group of 86 workers employed in three plants (A, B, and C) located in the same area and a control group of 26 employees of a Regional Hygienic Station (external control; EC) and 16 maintenance workers from plant B (plant control; PC). The mean styrene concentration in the workplace air, determined by personal dosimeters in three plants, was $81.3 \pm 56.3$ mg/m$^3$ (Table 4).

The corresponding styrene concentrations in blood were on an average found to be $0.56 \pm 0.43$ mg/L in the exposed group and $0.07 \pm 0.06$ mg/L in the control group, respectively (Table 4). In the control group, styrene concentrations in blood were exclusively recorded among the plant controls, suggesting that low-level, intermittent exposure to styrene might occur among the maintenance workers. Although these workers were not directly involved in the styrene processing,

Table 4
Some Characteristics of the Studied Population and Indicators of Exposure to Styrene (Vodicka, 2004)

| Characteristics | All exposed (n = 86) | Plant A (n = 35) | Plant B (n = 31) | Plant C (n = 20) | Plant controls (n = 16) | External controls (n = 26) |
|---|---|---|---|---|---|---|
| Age lyears (mean ± SD) | 36, 5 ± 12, 0 | 38, 5 ± 12, 6 | 38, 0 ± 12, 6 | 33, 7 ± 9, 5 | 48, 5 ± 7, 6 | 42, 8 ± 8, 2 |
| Sex (F/M) | 25/61 | 15/20 | 0/31 | 10/10 | 0/16 | 20/6 |
| Smoking habit | 44S/42 NS | 15 S/20 NS | 16 S/15 NS | 13 S/7 NS | 2 S/14 NS | 5 S/20 NS |
| Lifetime no. of cigarettes (mean ± SD) | 80, 771 ± 76, 529 | 59, 583 ± 64, 808 | 114, 850 ± 96, 236 | 2, 761 ± 45, 6420 | 127, 750 ± 5, 162 | 85, 600 ± 62, 591 |
| Years of employment (mean ± SD) | 4, 0 ± 4, 1 | 3, 4 ± 5, 3 | 5, 6 ± 3, 1 | 2, 5 ± 1, 9 | ND | ND |
| Workplace styrene exposure ($mg/m^3$ (mean ± SD) | 81, 3 ± 56, 3 (n = 73) | 112, 4 ± 57, 5 (n = 29) | 47, 1 ± 41, 9 (n = 27) | 82, 4 ± 43, 9 (n = 17) | ND | ND |
| Styrene levels in blood (mg/L (mean ± SD) | 0, 56 ± 0, 43 (n = 78) | 0, 71 ± 0, 47 (n = 34) | 0, 4 ± 0, 31 (n = 27) | 0, 50 ± 0, 44 (n = 17) | 0, 07 ± 0, 06 (n = 10) | ND |

Abreviations: F-female, M-male, ND-not determined, NS-Non smokers, S-smokers

the possible low-level styrene exposure of this group was further supported by the levels of urinary metabolites.

Unambiguously, the workers in styrene occupational areas are more at risk rather than other population. Further, it became obvious that people, living close to such plants, are comparatively less at risk than styrene workers although they are significantly exposed to risk (Vodicka, 2004).

A strong correlation between external and internal styrene exposure and styrene-specific urinary metabolites is well documented [10]. Thus, in exposed workers, the concentrations of styrene in the air were correlated with those in blood ($R = 0.817$, $p < 0.001$) (Vodicka, 2001).

Numerous epidemiological studies have evaluated the relationship between styrene and cancer in humans (Norppa, 1997). In the present paper we have considered the material reported by Harvard Center for Risk Analysis (Cohen, 2002) including amounts of styrene being present in air, food, water, consumer products, and waste materials. Mainly styrene is distributed by air. Thus, exposure through inhalation appears as the more important route.

The potential risk for styrene to be carcinogenic to humans were evaluated based on experiments studying mice and rats. These experiments displayed surprisingly that lung tumors were observed in mice but not in rats following long-term exposure (inhalation). Thus, it was established that female and male mice exposed to 20–160 and 40–160 ppm styrene, respectively, had a lung tumor incidence statistically higher than in the corresponding control group. On the other hand, similar experiment applying rats exposed to styrene concentrations as high as 1,000 ppm did not reveal an elevated incidence of lung tumors or at any other tumor incidences Cohen, 2002).

Effects of repeated styrene exposure observed in the lungs of mice, but not in rats, included focal crowding of bronchiolar cells, bronchiolar epithelial hyperplasia, and bronchiolo-alveolar hyperplasia, which may be responsible for the discrepancy in results (Cohen, 2002). Further, it is noted that the mechanisms of styrene genotoxicity are not fully investigated. However, it can be mentioned that QSAR/QSTR calculations (Pharma Algorithms) indicate that no significant 1st pass metabolism of styrene takes place, possibly associated with the significant binding probably to lipoproteins (predicted to be 78%, the logarithmic binding constant being 3.46). In the present report we shall not discuss the mechanistic aspects further, but just state that this discrepancy makes it increasingly difficult to extrapolate to humans. Thus, experimental results are inconclusive although suggestive for carcinogenic effects by styrene.

Studies have shown that workers in styrene production do display increased incidences of certain cancer forms. However, the studies are not unambiguous as other industrial exposures may have in influence as well (Cohen, 2002). Thus, also based on this, it was concluded that evidence for styrene's carcinogenicity in humans is "suggestive", meaning

that its carcinogenicity cannot be ruled out (Cohen, 2002).

Styrene further gives rise to a series of non-carcinogenic effects such as depression, drowsiness, headaches, disturbance of balance, hearing problems as well as problems with color vision. For further the Material Safety Data Sheet (MSDS), where all these effects have been summarized should be consulted.

#### 3.4.6.1 Quantitative Structure-Activity/Toxicity Relations

To further substantiate the above considerations we carried out a series of QSAR/QSTR calculations in order possibly to elucidate the toxic potential of styrene.

Styrene is predicted (Pharma Algorithms) to be virtually quantitatively absorbed passively in the human intestine through transcellular absorption, the corresponding absorption rate constant being found to be approx. 0.1 $min^{-1}$. There was no indication of active transport across the intestinal barrier (Pharma Algorithms) by the carrier proteins PepT1 (Sadee and Anderle, 2006) or ASBT (Dawson and Rao, 2006).

As mentioned above the major part, approx. 78% of the styrene appears as protein bound, probably to lipoproteins, which leaves a minor part, 22%, as the free species in the systemic circulation. Consequently, styrene may to a certain extent move freely throughout the body and thus travelling in and out of tissues the compounds may perpetrate its biological effects.

It is predicted (Pharma Algorithms) that styrene does not act as neither P-glycoprotein inhibitors nor as P-glycoprotein substrates. Thus, neither the possible transport to various organs nor the eventual efflux of the substances appears to be mediated by active P-glycoprotein transporters.

Experimental studies on the possibly genetoxicity of styrene appear inconclusive and the possibility for styrene to result in a positive Ames test is only 21% (Pharma Algorithms). On the other hand, the possible carcinogenicity of styrene must be taken into account. Thus, it was estimated (PASS1) that the overall probability for styrene to be carcinogenic is approx. 53%, composed by carcinogenic, group 2A 47%, carcinogenic, group 2B 41% and carcinogenic, group 66%, respectively. The corresponding probabilities for styrene not to exhibit these effects were calculated to be 2, 3, and 1%, respectively. Further, it is worthwhile to note that our calculations (PASS1) nicely mimicked the above mentioned discrepancy between mice and rat. Thus, the probability for styrene to be carcinogenic to female and male mice respectively was predicted to be 55% and 43%, respectively, whereas the analogous value for male rats was determined to be only 38%. The probabilities for not showing these effects were 2, 5 and 8%, respectively.

This series of QSAR/QPSTR calculations (PASS1) further indicated that styrene may be tetratogen (56/6) as well as toxic (cardiotoxic: 46/16; hematotoxic: 97/1; embryotoxic: 55/4), the values given corresponding to the probabilities (in pct.) for exhibiting/not exhibiting the given effect.

Further it was estimated that styrene is skin irritating (high: 49/1; moderate: 87/1) and eye irritating (high: 47/2; weak: 84/1) in nice agreement with the information at the Materials Safety Data Sheet (MSDS).

The probabilities for adverse organ effects appear relative low. Thus, it was calculated that the probabilities for styrene to cause adverse health effects on blood, the cardiovascular system, the gastrointestinal system, kidneys, liver and lungs amounts to 18, 13, 9, 12, and 10%, respectively (Pharma Algorithms), possibly reflecting the sometimes inconclusive experimental studies.

The acute toxicity of styrene is low. Thus, for both intraperitoneal, oral and subcutaneous administration the calculated values are calculated to be above 4–500 mg/kg for both mice and rats in good agreement with experimental data (Pharma Algorithms). Only in the case of intravenous administration (mice) a somewhat lower values (71mg/kg) was calculated. However, this is still a pretty high dose.

#### 3.4.6.2 Margin of Exposure

To determine whether human exposure to styrene is high enough to warrant concern if styrene turns out to be carcinogenic, the panel estimated the "margin of exposure" (MOE) for several exposure scenarios. The Margin of Exposure (MOE) is expressed as the ratio between the harmfulness of the substance, given as the so-called Bench Mark Dose, $BMDL_{10}$, (EPA, 1995, 2008b; Fitzgerald et al., 2004), which is the value expected to give a rise in cancer incidents by 10%, and the exposure to the toxic chemical ($E_c$) (ESFA, 2005).

$$MOE = \frac{BMDL_{10}}{E_c}$$

According to the recommendations of European Food Safety Authority, EFSA, (ESFA, 2005) special precautions and possible actions have to taken in case where substances display a MOE < 10.000, whereas substances with a MOE > 10.000 can be down-prioritized.

In the case of styrene the experiments on mice were used as background for setting human equivalents. Thus, it was estimated that doses corresponded to atmospheric concentrations between 2–20 ppm would apply (Cohen, 2002). The MOE's calculated based on 3 scenarios applying $BMDL_{10}$ values of 2, 5 and 20 ppm, respectively, is shown in Table 5 for 4 groups supposed to have average life time exposures of 1, 6, 3, and 220 ppb styrene, respectively.

It is immediately noted that in relation to carcinogenic effects virtually all values are found to be below 10.000, thus calling for immediate concern

Table 5
Non-ocupational Margins of Exposure (Cohen, 2002)

| | | Cancer MOE corresponding to a comparison dose producing in estimated 10% increase in mouse lung tumour incidence | | |
|---|---|---|---|---|
| | Lifetime average exposure | Low-end comparison dose values 2 ppm | Most likely comparison dose values 5 ppm | High-end comparison dose values 20 ppm |
| Typical ambient exposure | 1 ppb | 2 000 | 5 000 | 20 000 |
| Exposure to styrene from lifetime smoking | 6 ppb | 400 | 800 | 3 000 |
| Living 100 meters from a hypothetical 100,000 pound per year emission facility (high exposure scenario, 95 percentile individually) | 3 ppb | 700 | 2 000 | 7 000 |
| Living at the point of greatest exposure in the vicinity of a hypothetical 1 million per year emission facility (high exposure scenario, 95 percentile individually) | 220 ppb | 10 | 20 | 100 |

(ESFA, 2005), whereas in the case of non-carcinogenic effects, only the group living in the direct vicinity of the production plant appears to be in immediate danger.

For non-carcinogenic effects the lowest exposure level at which color vision in workers was affected was established to be 50 ppm (Cohen, 2002), the corresponding MOE's for the 4 groups mentioned in Table 5 being 50.000, 8000, 17.000 and 230, respectively.

### 3.5 Responses

Based on the above discussed studies, even taking uncertainties and low calculated percentages of toxic actions into account, it appears unambiguous that the possible impact of styrene, due to deliberate or accidental release call for attention in order to minimize and possibly eliminate any hazardous influence on the environmental and human health.

Obviously, the main question is emission control and reduction and it appears necessary that this question must be brought into play in all phases of the planning and eventually the construction of the proposed production plant. In this connection it appears mandatory that the authorities set up relevant and appropriate threshold limits both for the work environment and for the external environment in order to prevent hazardous influences of workers, the environment and the neighboring residents.

In addition to this appropriate measures in relation to the personal protection of the workers must be taking, such as skin and eye protection as a minimum as also recommended in the Material Safety Data Sheet (MSDS).

Obviously, it is mandatory to set up an appropriate monitoring system covering both the work environment and the external environment. Hence, in sum appropriate responses comprise:

- Emission control and reduction measures.
- Establishment of appropriate threshold limit for the work environment.
- Establishment of appropriate threshold values for the external environment.
- Requirement for workers to use appropriate personal protection equipment.
- Setting up an appropriate monitoring system for the work environment.
- Setting up an appropriate monitoring system for the external environment.

A detailed discussion of the above mentioned responses, e.g. details on the monitoring systems are outside the scope of the present study, as the responses will be strongly linked to the actual construction phase as well as the subsequent production phase.

## 4. CONCLUSIONS

Styrene is one of the most frequently used monomers in the polymer industry and as such major production facilities apparently is necessary in order to comply with the constantly increasing demands for raw materials. In this context an ongoing project to establish a major styrene producing plant in Kazakhstan calls for attention as styrene may adversely affect both the environmental and human health in case of deliberate or accidental releases of monomeric styrene.

The present paper summarizes, within the frame of the DPSIR framework, a series of previously published studies on styrene in combination with a series of QSAR/QSTR calculations in order to collect the necessary data for a preliminary risk assessment of styrene.

From our studies it appears evident that although the acute toxicity of styrene is relatively low a series of adverse effects, including carcinogenicity, teratoxicity and embryotoxicity may very well occur in addition to effects like skin and eye irritation. On the other hand we find that the probabilities for adverse organ effects in general are low.

Based on the data collected it is strongly emphasized that the questions of emissions of styrene must be taken into consideration during all phase of the construction of the production plant and subsequently, when the plant is in operation emissions of styrene must be controlled and monitored during all stages of the production. Thus, setting threshold limits for the emissions of styrene and the establishment of an appropriate monitoring system appears mandatory measures.

Personal protection equipment must be used by the workers.

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