Post-Emergency, Multi-Hazard Health Risk Assessment in Chemical Disasters
PEC

Deliverable D.D.2

Risk maps for long-term health effects

ECHO/SUB/2015-713844-PREV11 - PEC: Post-Emergency, multi-hazard health risk assessment in Chemical disasters
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EXECUTIVE SUMMARY

To assess the long-term health impacts associated with exposure to benzene, acrylonitrile, arsenic and cadmium, a comprehensive methodology was developed, that takes into account exposure and internal dose dynamics through physiology based biokinetic modelling, coupled with biology based dose response for carcinogenicity. The overall exposure and risk assessment of releases of compounds with different physico-chemical and toxicokinetic properties is greatly facilitated by the use of integrated exposure computational platforms, able to capture the dynamics of environmental fate, the contribution of the relevant exposure pathways and the respective lifetime internal dose, accounting as well for age and gender related differences.

Using this comprehensive methodology, risks were estimated for the various incidental events in Plant A and Plant B. Based on the results, regarding Plant A gaseous emissions show the highest impacts during the winter season while liquid emissions show higher impacts during the summer. This behavior can be explained considering that during winter, the mixing height is lower, resulting in higher exposure levels, while in the summer, the higher temperatures favor evaporation, resulting in higher airborne releases. This is the case for all compounds characterized by high vapor pressure included in the analysis (benzene, acrylonitrile and arsenic), but not for cadmium. Regarding Plant B, risks associated to arsenic and the related health impacts are the highest ones (among all the compound release incidents), as the result of the very high toxic potency. Hence, the long-term health effects of the various site-specific cancers, are expected to derive the highest health impacts among the various scenarios investigated in PEC. It has also to be noted that cancer risks associated with arsenic are differentiated within genders; overall, males are subjected to an almost 20% higher risk compered to women, due to differences in metabolism and response to arsenic metabolites. Regarding cadmium releases in Plant B, the estimated risk and the associated health impact are practically negligible. This is the result of the very low vapor pressure that does not favor the distribution and transportation in airborne media. Potential uptake related to cadmium release is associated only with non-dietary ingestion of soil, excluding any other inhalation, dermal or dietary ingestion pathway.

It has also to be noted, that the health risks associated with an accidental event in some cases exceeded the background environmental risks of the related compounds. This shows that short-term exposure events of none persisting compounds resulting from accidents or malicious actions, are able to pose significant long-term health risks. It worth also to be highlighted that the lifetime cancer risks of the children are more than 70% higher compared to the one of adults exposed to the same levels of contamination, as a result of the highest bodyweight normalized inhalation rate which in turn results in higher uptake and internal dose of the toxic compounds and their metabolites.

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1 ESTIMATING LONG TERM CANCER HEALTH EFFECTS

1.1 Rationale of key industrial compounds carcinogenicity

1.1.1 Benzene

There is sufficient evidence in humans for the carcinogenicity of benzene, as a series of cohort and case–control studies associated occupational exposure to benzene and benzene-containing solvents with leukaemia (IARC, 1982). IARC classified benzene as a Group-1 carcinogen, citing evidence of an increased incidence of Acute Non-Lymphocytic Leukaemia (ANLL) in workers exposed to benzene in three cohort studies (IARC, 1987). Since 1987, there have been numerous reports from cohort studies in populations exposed to benzene, including reports and new case–control studies of leukaemia or its subtypes in adults and children, as well as non-Hodgkin lymphoma (NHL), multiple myeloma, and to a lesser extent other tumours in adults. Many studies have shown evidence of the appearance of acute myelogenous and monocytic leukaemia as well as ANLL in people exposed to benzene in various industries and in several countries (Bloemen et al., 2004; Guenel et al., 2002; Hayes et al., 1997; Kirkeleit et al., 2008). Non-Hodgkin Lymphoma (NHL) is a heterogeneous group of histological subtypes. The definition of these subtypes has evolved over the last years, which complicates the assessment of exposure to benzene and risk for NHL. Data on histological subtypes of NHL have generally not been reported in publications of occupational cohort studies of benzene-exposed workers, but they have been mentioned in some case–control studies. For various benzene-exposure metrics, non-significant risks for NHL were found in most studies (Fabbro-Peray et al., 2001; Rinsky et al., 1987b). One subtype of NHL is Acute Lymphocytic Leukaemia (ALL) according to WHO classification of lymphomas. A non-significantly increased risk for ALL was indicated in multiple cohorts, but the numbers of cases were small (Gun et al., 2006; Rushton, 1993). Furthermore, several studies in the petroleum industry and in other settings, as well as case-control studies have shown non-significantly increased risks for Chronic Myelogenous Leukaemia (CML), whereas other studies show no evidence of an association between benzene exposure and the appearance of CML (Adegoke et al., 2003; Guenel et al., 2002). The same findings were established by most cohort and case-control studies for Multiple Myeloma (MM). In the case of Chronic Lymphocytic Leukaemia (CLL), several cohort studies in the petroleum industry showed mixed results, with some non-significantly increased risks reported and other studies showing no association. There are sparse data on Hodgkin disease in studies of benzene-exposed cohorts, with most studies having very small numbers of cases and showing no association. Overall, there is no evidence of an increased risk. The relatively few case–control studies in adults also show no association. From the evaluation of the cohort studies that provided data on cancer sites, it was apparent that exposure to benzene was associated to malignant melanoma (Lewis et al., 2003; Schnatter et al., 1996), nose, stomach and prostate cancer (Fu et al., 1996).

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1.1.3 Acrylonitrile

Several cohort epidemiology studies evaluated a number of health outcomes, including cancer, in workers exposed to acrylonitrile (AN). Detailed results were provided for the lung, bladder, prostate, and central nervous system cancers, which have received the most attention (Benn and Osborne, 1998; Blair et al., 1998; Mastrangelo et al., 1993; Swaen et al., 2004; Swaen et al., 1998; Wood et al., 1998). IARC (1999) summarized and evaluated the findings of these reports and concluded that there was no significant excess risk for any type of cancer when all exposed workers were compared with unexposed, or with external comparison population. Furthermore, when the study subjects were subdivided by levels of exposure (cumulative exposure when feasible), for no site but lung was there any hint that risk increased with exposure. For lung cancer, there was an indication that workers with the highest exposures had relative risk estimates greater than 1. This finding was strongest in the largest of the studies, which had one of the most intensive exposure assessment protocols, but the other gave either negative or only weakly positive results (O'Berg, 1980). On balance and given the largely unsupportive findings from the other studies, the evidence from this one study was not considered to be sufficiently strong to conclude that there was a credible association between AN and lung cancer (Chen et al., 1988; O'Berg et al., 1985). Thus, the earlier indications of an increased risk among workers exposed to AN were not confirmed by the recent, more informative studies. In summary, most of the results did not support a causal relationship between AN and all cancers or any specific type of cancer. This is the reason that IARC downgraded acrylonitrile from "probably carcinogenic" to "possibly carcinogenic to humans" finding that "the earlier indications of an increased risk among workers exposed to acrylonitrile were not confirmed by the recent, more informative studies" (Cole et al., 2008). However, there are epidemiological findings that still suggests the possibility of causal association between very high exposure to AN and lung cancer in humans. It may also be concluded that degree of carcinogenic potential of AN is rather weak, if any, to humans because no clear evidence of cancer excess could be found by recent cohort studies with longer follow-up and larger observed population (Sakurai, 2000).

1.1.4 Cadmium

The assessment of cancer risks in occupational cohorts exposed to cadmium is constrained by the small number of long-term, highly exposed workers, the lack of historical data on exposure to cadmium and the inability to define and examine a gradient of cumulative exposure across studies. Few studies could control the confounding effect of co-exposure to other substances, particularly arsenic and nickel; however, the analyses of workers with low levels of exposure to arsenic still showed an increased lung cancer risk associated with cadmium exposure. Additional support for a cadmium-linked lung cancer risk comes from a prospective population-based study in environmentally polluted areas in Belgium (Nawrot et al., 2006). The results of the studies on cadmium exposure and the risk of prostate cancer are suggestive of an association, but the results are inconsistent. In studies of occupational cohorts exposed to cadmium, studies of people residing in cadmium-contaminated areas and case–control studies of individuals with prostate cancer, some

studies reported an increased risk for prostate cancer, while other studies did not indicate the same (Armstrong and Kazantzis, 1985; Sahmoun et al., 2005; Sorahan and Esmen, 2004). The results from cohort studies are supported by a hospital-based case–control study that included highly exposed subjects (Vinceti et al., 2007). Case–control studies suggest that other cancer sites, such as the kidney, and perhaps also the bladder, the breast, and the endometrium may show increased risks associated with dietary or respiratory cadmium exposure (Åkesson et al., 2008; Antila et al., 1996; Hu et al., 2002; Jarup et al., 1998; Kriegel et al., 2006; Pesch et al., 2000; Sorahan and Esmen, 2004). The International Agency for Research on Cancer reevaluated the evidence for carcinogenicity of cadmium in 2009 and reaffirmed its earlier conclusion that there was sufficient evidence of cadmium's carcinogenicity in humans. The evidence was classified as sufficient for lung cancer and limited for prostate and kidney cancer (Straif et al., 2009).

1.1.5 Arsenic

The toxicity of arsenic, including cancer, is most likely due to multiple mechanisms. The mechanisms responsible for the adverse effects associated with arsenic, probably occur through multiple independent and interdependent mechanisms (Duker et al., 2005; NRC, 2001). Two general types of mechanisms appear to be involved in arsenic-induced toxicity: (1) formation of reactive oxygen species (ROS). Arsenic can disrupt the oxidative phosphorylation, leading to free radical formation. Pentavalent arsenic may be transformed to a substitute for inorganic phosphate in glycolysis, leading to uncoupling of oxidative phosphorylation and loss of ATP formation (TOXNET, 2016). Arsenic-induced ROS generation has been associated with numerous effects on cellular targets (Hubaux et al., 2013), which can directly damage cellular components or lead to a cascade of effects in response to oxidative stress (alterations in intracellular oxidation/reduction reaction, decreased glutathione levels, lipid peroxidation, damage to proteins, disruption of mitochondrial membrane, genomic instability through damage to DNA). The current consensus in studies with cultured cells, experimental animals, and humans is the fact that arsenic causes oxidative stress through the generation of reactive oxygen species (Fujino et al., 2005; Kumagai and Sumi, 2007). (2) interaction of arsenic metabolites with cellular macromolecules. Arsenic can interfere with essential enzymatic functions and transcriptional events in the cells. Inorganic arsenic exerts epigenetic effects (Bodwell et al., 2006; Reichard et al., 2007). Trivalent species are more potent cytotoxicants, genotoxicants and inhibitors of enzymes compared to pentavalent arsenicals (El-Masri and Kenyon, 2008). One of possible mechanisms for higher toxicity is the higher affinity for thiol compounds (Shiobara et al., 2001) and generation of reactive oxygen species (Nesnow et al., 2002). Exposure to inorganic arsenic has been shown to modify the expression of a variety of genes related to cell growth and defense, including the tumor suppressor gene p53, as well as to alter the binding of nuclear transcription factors (TOXNET, 2016).

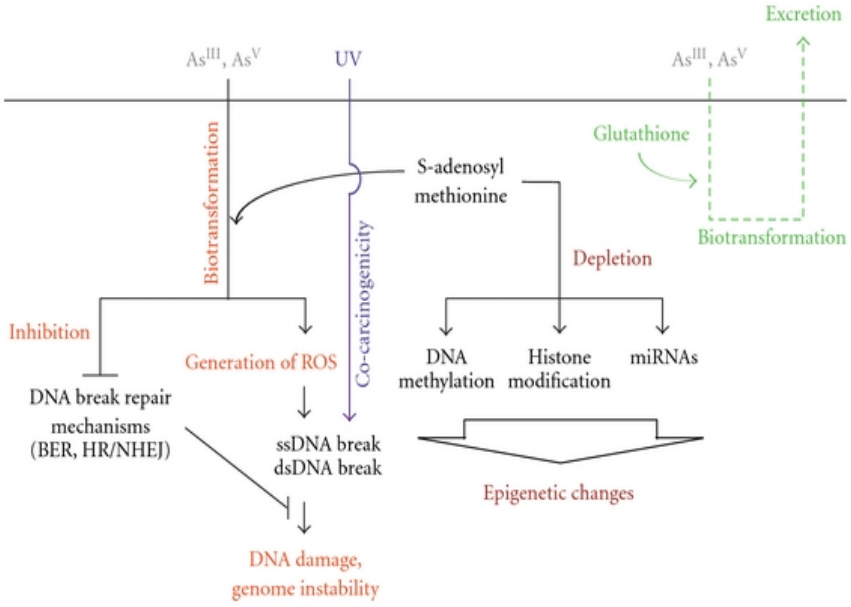

Figure 1. Carcinogenic mechanisms of arsenic transformation.

Figure 1 explains how ingested arsenic undergoes biotransformation process and how those can result to carcinogenic activity. (1) Biotransformation could lead to arsenic excretion, when conjugated with glutathione. (2) Biotransformation generates reactive oxygen species (ROS), that induce single-strand (ssDNA) and double-strand (dsDNA) breaks by inducing oxidative damage. The process can also inhibit DNA break repair mechanisms (Martinez et al., 2011). Additionally, ROS can act as co-carcinogens. Furthermore, the requirement of S-adenosyl methionine (SAM) for arsenic biotransformation can lead to depletion of SAM, which is the substrate for DNA methylation. Recently, a study showed that exposure to arsenic triggers a shift in microRNA expression and revealed an induction of cell cycle progression and failure of apoptosis supporting the idea of inorganic arsenic carcinogenic activity (Sturchio et al., 2014).

Unlike many carcinogens, arsenic is not a mutagen in bacteria and acts weakly in mammalian cells, but can induce chromosomal abnormalities, aneuploidy, and micronuclei formation. In vitro studies showed that As^{III} exposure to humans from drinking water can lead to the formation of micronuclei (Johnson, 2007). Arsenic can also act as a co-mutagen and/or co-carcinogen (Casarett and Klaassen, 2008). Although a large amount of research is available on arsenic's mode of action, the exact nature of carcinogenic action is not yet clear (NRC, 2001). The proposed Mode of Action include alteration in DNA repair, change in DNA methylation, suppression of cell cycle check point protein (p53), altered expression of growth factor and oxidative stress. Inorganic arsenic has been classified by the IARC (IARC, 1973) in Group 1 as carcinogenic to humans on the basis of increased incidence of cancers at several sites where people were exposed. IARC (2004) has classified arsenic as a known human carcinogen, associated with tumors of the skin, lung, and urinary bladder, and possibly kidney,

liver, and prostate. A ranging risk of 10^{-4} to 10^{-7} was developed by EPA (ATSDR, 2007). An established association between human arsenic exposure and human cancer has been known for many years (Chen et al., 1992; Wu et al., 1989). A clear dose-response relation between Arsenic and drinking water for cancer in kidney, lung and bladder has been reported in Argentina (Hopenhayn-Rich et al., 1998) and a high lung cancer mortality in Japan (Tsuda et al., 1995). Arsenic is contributing to cancer (Bernstam and Nriagu, 2000; Clewell et al., 1999) of the skin (Yu et al., 2000), lungs (Ferreccio et al., 2000; Lubin et al., 2000), kidney, liver and bladder (Bates et al., 1992; Chen and Wang, 1990; Smith et al., 1992). Trivalent methylated arsenicals are responsible for the toxicity and carcinogenicity of environmental arsenic (Hirano et al., 2004; Nesnow et al., 2002). MMA^{III} and DMA^{III} have been suggested as potential contributors to arsenic-induced carcinogenicity (Bernstam and Nriagu, 2000; Kitchin, 2001). DMA^{V} on the other hand, is a urinary bladder carcinogen and tumor promoter in rats (Cohen et al., 2006). The most common pathway of exposure to inorganic arsenic for the general population is via the drinking water. Early effects of exposure to arsenic in drinking water included pigmentation changes and hyperkeratosis (Alam et al., 2002; Mazumder et al., 1998; Smith et al., 2002). These skin lesions may develop into more serious and disabling forms, including cancer (Haque et al., 2003).

1.2 Methodology for estimating cancer risk associated to long term exposure based on internal dose

1.2.1 Biology based dose response models

1.2.1.1 General concept

For assessing risks for long term effects, a mechanistic approach will be followed when adequate data exist, allowing us the development of a BBDR (Biology Based Dose Response) model, linking exposure, to internal dose and following the modeling of a biological process leading to adverse health effects.

BBDR may be derived mainly in two ways:

- By describing with a purely mechanistic procedure a sequence of biological events that may lead to the adverse outcomes and in this case, all kind of toxicological data may be necessary.
- By linking epidemiological data to internal dose.

To derive a quantitative health risk estimate regarding cancer, we can apply a multistage approach derived from the work of Armitage and Doll (1954; 1957) and based on the decomposition of the dose-response relationship into different micro-relations each one describing a specific biologic process (Figure 2).

Instead of trying to quantify the relation between dose and response probability directly, it is useful to decompose the causal relation between exposure history and health risk probability into biologically meaningful causal links called "micro-relations" to quantify these links, and then to estimate the full dose-response relation by combining its constituent micro-relations.

As an example, the dose-response relation for benzene can be described as the composition of two micro-relations, one linking administered dose (or the external exposure) to internal dose of benzene metabolites, the other linking internal dose to cancer risk.

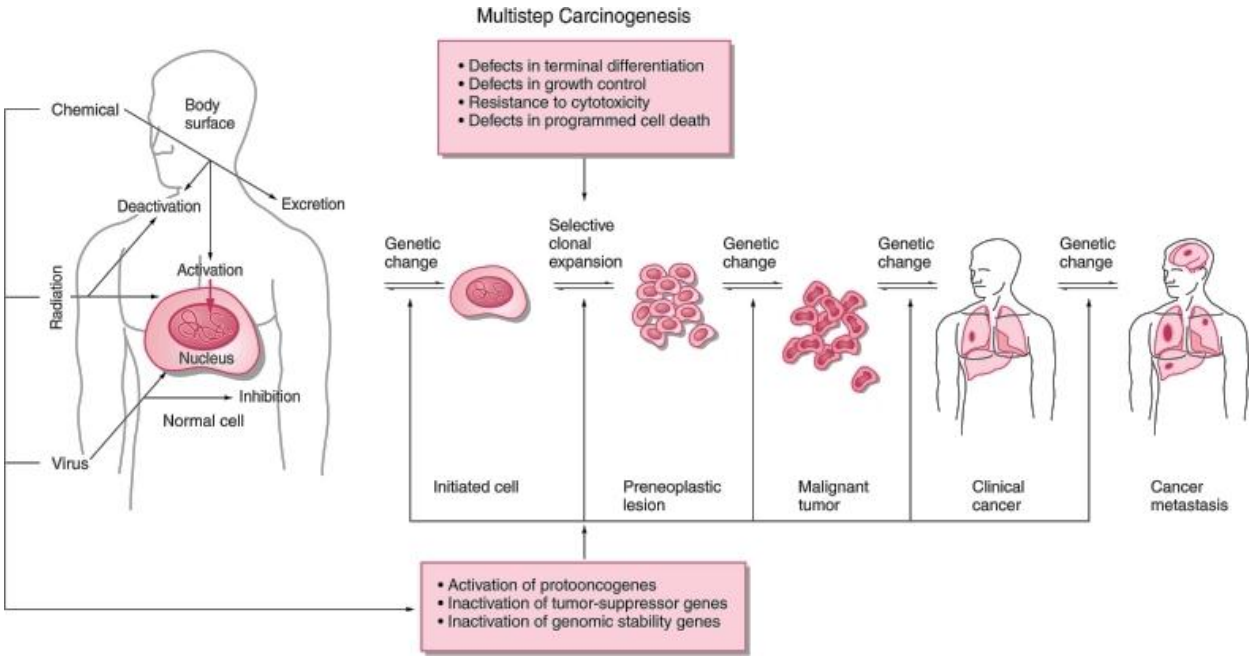

Figure 2. Multi-stage carcinogenesis (NCBI, 2010)

To discuss how the multistage model may be used to improve risk assessment, it can be useful to introduce the notation:

$(a \parallel b)$ = time history of quantity ***a*** determined by the time history of quantity ***b***

This notation is intended to imply that ***a*** and ***b*** are time-varying quantities, with the history of ***an*** up to and including any moment ***t*** being completely determined by the history of ***b*** up to the same moment.

Taking as example the case of benzene, the dose-time-response relation between benzene exposure and AML risk may be denoted by:

$(p \parallel x)$

to indicate that the probability of tumor at time ***t*** is determined by the history of arsenic exposures up to time ***t***. Another suggested notation for a closely related concept is

$\{x\} \rightarrow \{p\}$

read as "the history of ***x*** determines the history of ***p***."

By contrast, $\{p \parallel x\}$ might be read as "the history of ***p*** that is determined by the history of ***x***." The curly brackets enclose individual time-varying quantities, or histories.

Now, suppose that AML risk depends on arsenic exposure only because of the formation of one or more arsenic metabolites. Letting $\{y\}$ denote the history (i.e., the time course) of the vector of metabolites in different physiological compartments over time, the causal situation may be represented as

$$\{x\} \rightarrow \{y\} \rightarrow \{p\}$$

In other words, $\{x\}$ determines $\{y\}$ and $\{y\}$ determines $\{p\}$. Thus, the administered dose-time-response relation $(p \parallel x)$ may be decomposed as

$$(\{x\} \rightarrow \{y\})^{*}(\{y\} \rightarrow \{p\})$$

where * is the composition operator for composing consecutive mappings. This decomposition, based on internal dose of metabolites, may be expressed in the equivalent form

$$(p \parallel x) = (p \parallel y) * (y \parallel x)$$

The component $(y \parallel x)$ corresponds to the input-output relation of a physiologically based pharmacokinetics (PBPK) model, i.e., it maps exposure dose histories $\{x\}$ into resulting time courses $\{y\}$ of benzene metabolites in different physiological compartments.

The micro-relation $(p \parallel y)$ represents an internal dose-response function to be derived from statistical regression analysis based on experimental data on metabolite levels and toxicity endpoint rates.

This relation has in most cases the shape of quadratic or cubic upward curve such as:

$$P(y) = 1 - \exp(ay + by^2 + cy^3)$$

where *P(y)* denotes the probability of the event, a, b and c are coefficients determined through a statistical model and *y* represents the internal dose.

In this way dose-response relationships that can appear unclear or confusing at the administered dose level (external exposure) can become more understandable when expressed on the basis of internal dose of the chemical. The major advantage of constructing dose-response relationships on the basis of internal or delivered dose is that it can provide a stronger biological basis for conducting extrapolations and for comparing responses across studies, species, routes, and dose levels (Andersen et al., 1987; Aylward et al., 1996; Benignus et al., 1998; Melnick and Kohn, 2000).

1.2.1.2 Benzene

The final building block for addressing the source to health outcome continuum is the definition of mathematical models of human pathology. Pathology modeling has focused on a few ill-health conditions such as cancer and organ malfunction (e.g. heart disease) to date. This approach varies from a purely phenomenological one, including statistical descriptions of the link between toxic insult and health effect, to sets of differential equations describing mechanisms of action and partial differential equation models that take into account the presence of xenobiotics in specific parts of

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organs, up to more advanced mathematical techniques including cellular automata, neural networks and other artificial intelligence methods for quantifying the link.

According to Schollnberger et al (2006), the earliest approaches to mathematically investigate cancer began in the early 1950s. Nordling (1953) and Stocks (1953) proposed that several successive mutations in a cell would be necessary to explain the fact that, for many carcinomas, the incidence rate varies as a power function of age. This has been quantitatively formulated by Armitage and Doll (1954b) in one of the best-known cancer models, a multi-stage model that accounts for the relationship between age and cancer incidence. The model reflects the number of stages needed for a normal cell to develop into a malignant cell. For the Armitage–Doll multi-stage model, no clonal growth was assumed. Because of discrepancies with the observed number of biological stages, Armitage and Doll further developed their model into one of two stages, with exponentially growing clones (Armitage and Doll, 1957). The Armitage–Doll two-stage model has limitations in cancer risk assessment because it assumed deterministic cell growth. When the growth rate is small, it is more appropriate to use a stochastic model because the probability of extinction of clones, which is not considered in a deterministic model, cannot be neglected. This led to the development of stochastic cancer models (Knudson Jr, 1971; Moolgavkar, 1978; Moolgavkar and Knudson Jr, 1981; Moolgavkar and Venzon, 1979; Tan, 1991). Stochastic cell growth of intermediate cells is assumed for the stochastic two-mutation model with clonal expansion. This two-step clonal expansion (TSCE) model is the best-known multi-step model and was developed by Moolgavkar, Venzon and Knudson (Moolgavkar, 1978; Moolgavkar and Knudson Jr, 1981; Moolgavkar and Venzon, 1979), after whom it is known as the MVK model. In contrast with the Armitage–Doll model, there is a considerable amount of experimental data supporting the stochastic two-mutation model (Chen, 1993).

Among the four VOCs considered in this work, benzene represents certainly the most potentially dangerous to human health. Chronic exposure to low levels of benzene may produce reversible decreases in blood cell numbers but, at higher levels, an irreversible bone marrow depression, with pancytopenia, may establish. This pathological condition is called aplastic anemia. Pancytopenia can occur also in the so-called myelodisplastic syndrome (MDS). Benzene MDS usually proceeds to leukemia, mostly acute myeloid leukemia (AML). The approaches taken to assess the cancer risk from benzene exposure have been varied and have resulted in risk estimates that range considerably in magnitude. The U.S. EPA (2000) used the Goodyear Pliofilm study (Rinsky et al., 1987a; Rinsky et al., 1981) for their quantitative risk estimation. They estimated a range of $2.2 \cdot 10^{-6}$ to $7.8 \cdot 10^{-6}$ as the increase in the lifetime risk of an individual who is exposed for a lifetime to 1 ug/m^3 benzene in air. This is based on a linear model and extrapolates to air concentrations of 1.3 to 4.5 ug/m^3 for a risk level of 1 in 100,000. The approach used by Crump directly linked external exposure to cancer risk using the Area Under the Curve (AUC) as the dose metric. Finally, an empirical statistical D-R model based on Maximum Likelihood Estimation (MLE) is derived, based on experimental data about cancer incidence as function of the exposure. The dose-response model developed by Crump (1994) takes the following form:

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$$P(x) = 1 - e^{\left[-\left(0.00145x + 0.00013x^2\right)\right]}$$

where ***P(x)*** represents the cancer probability attributable to ***x*** mg/kg/day of administered benzene to male mice. This equation implies that, at very low administered doses, the risk varies linearly with dose. To extend it to humans the authors of this study assumed that the same administered quantities of benzene "produce equal cancer risk in humans and animals, independent of the route of exposure". A key weakness of this approach is that AUC might not be the best choice of dose metric for benzene since it does not distinguish between dose histories having different time evolution if they have the same integrated total dose. For these situations the risk estimate based on the AUC will produce the same risk, although many experiments have shown that different time patterns of benzene dose administration with the same AUC produce very different profiles of benzene metabolites (Crump and Allen, 1984) and very different hematotoxic effects. In this work we applied a method, originally developed by Cox Jr. (1996), based on the decomposition of the dose-response relationship into a set of causal micro-relations, each one describing a separate biologic process. Instead of evaluating the relationship between administered dose and cancer risk 'directly' through an empirical-statistical model, this relationship is thus decomposed into two different parts: the first one links the administered dose to the total amount of metabolites produced (internal dose), while the second connects the internal dose to the probability of cancer. The first relation is provided by the results of the PBPK/PD model, which has already been validated against human biomonitoring data (Sarigiannis and Gotti, 2008). The statistical relation between internal dose and cancer probability was calculated using a parameterized function (1) from Crump and Allen (1984). In particular, the administered dose was calculated assuming an average person of 70 kg (adult) who inhales 10 m^3 of air in 8 hours for an occupation period of 40 years over a life of 70 years. The next step was to derive an empirical statistical relation linking the internal dose to cancer probability. This was found to be the following:

$$P(y) = 1 - e^{\left[-0.04296940\,y + 0.02633730\,y^2 - 0.00764081\,y^3\right]}$$

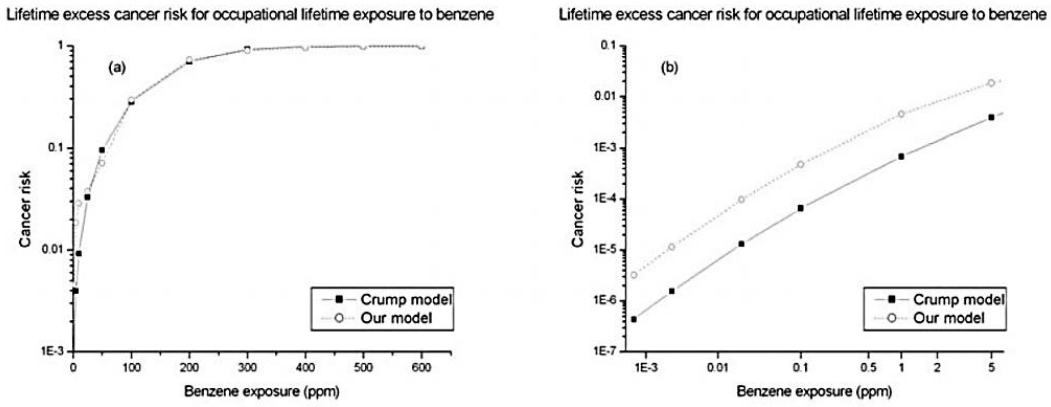

Figure 3 (a) lifetime excess cancer risk for 8hr/day lifetime inhalation exposure to benzene as predicted by Crump and Allen and our model. (b) the same at low doses

The standard error for the model parameters varied from 23% (for the linear term) to 9% (for the cubic term). This relationship incorporates the results of the PBPK/PD models that allow us to estimate the actual biologically effective dose (BED) of benzene metabolites in the bone marrow (the main target tissue for leukemia). BED of benzene metabolites is associated with the intake dose of both benzene and other VOCs present in the BTEX mixture. It has to be noted, however, that metabolic inhibition of benzene by co-exposure to toluene, ethylbenzene and xylenes is dose-dependent. This kind of biochemical interaction is usually low at very low levels of exposure. Thus, cancer probability, ***P(y)***, can be linked mathematically to the average benzene exposure level, ***y***, even though the cancer potency of benzene is attributed to its metabolites. In Figure 3 the estimated cancer risk as a function of the external benzene concentration as predicted by Crump and Allen model (solid line) and by our model (dashed line) is given.

1.2.1.3 Arsenic

Dose-response assessment, is the estimation of the relationship between dose or level of exposure to arsenic, and the incidence of an effect (Leeuwen, 2007). BBDR models provide the substrate for simulations that link mode of action research with predicted physiological consequences of exposures (Andersen et al., 2002). Once the internal doses are calculated via the PBPK model, the next step is to link the internal dose with the health point considered to assess the quantitative risk associated with the given exposure (Clewell et al., 2007; Conolly and Andersen, 1993). The result is a quantitative estimate of health risk relevant to specifics health end-points in the exposed population.

A risk assessment not taking into account the different species but considering only total arsenic, would lead to a considerable overestimation of the health risk related to arsenic exposure (Chain, 2009), therefore it is required to relate the toxicity of all the forms of arsenic found in the PBPK model, to the toxicity of the trivalent arsenic. An in vitro study with human epidermal keratinocytes showed the relative toxicities: $As^{III} > MMA^{III} > DMA^{III} > DMA^{V} > MMA^{V} > As^{V}$ (Vega et al., 2001). Among the different forms in which arsenic can be found, the most toxic is arsenite, followed by arsenate, then the two organic metabolites. However, more recent studies report that the trivalent form of MMA and DMA are likely to be as biologically active as arsenite. Thus, the toxicity order of Arsenic metabolites may be described as follows: DMA^{III}, $MMA^{III} > As^{III} > As^{V} > DMA^{V}$, MMA^{V}> *TMAO*. In general, the toxicity of pentavalent species is lower than that of trivalent by the order of 10^{-3} to 10^{-4} (Hirano et al., 2004; Vega et al., 2001). This may be explained by the faster uptake rate of As^{III} in endothelial cells (Hirano et al., 2003).

Table 1-1.Relative toxicity of arsenic species to trivalent inorganic arsenic.

Arsenic form	AsIII equivalent mole (for 1 mole of compound)	Toxicity
Arsenite – As(III)	1	1
Arsenate – As(V)	1	1/35
Trivalent Monomethylarsonate MMA(III)	0.605	1
Pentavalent Monomethylarsonate MMA(V)	0.536	1/85
Trivalent Dimethylarsinate DMA(III)	0.620	1
Pentavalent Dimethylarsinate DMA(V)	0.543	1/85

Steps for using PBPK model estimated Internal Dose in Dose-Response Model for arsenic was (Andersen et al., 2005):

- Identify toxic effects in people, and determine health endpoints from experimental data associated with arsenic exposure
- Use an appropriate PBPK model to estimate the internal tissue dose metric for various routes of administration, at various doses, for specific exposure scenarios
- Development of a dose-response model based on the relationship between internal dose and health points.
- Estimate the probability of the health risks in humans based on the internal tissue dose calculated during human exposures

Step three allows us to develop and parameterize a three-stage model (administered dose-internal dose-cancer probability) for cancer growth that links internal doses to health risk probability. In developing BBDR models it is necessary to evaluate the effect of dose on biological parameters of the model. The effects can be described empirically, as has usually been done, or mechanistically. For the cancer models the stochastic aspect involves some probability of division, death, or mutation that occurs randomly (Andersen et al., 2002). Trying to quantify the relation between dose and response probability, it is useful to decompose the relation between exposure and health risk probability. In this case one relation links the administered dose to the internal dose of arsenic and its metabolites, the other links internal dose to cancer probability. In probabilistic terms it can be explained as follows (Armitage and Doll, 1954a).

The dose-response relation between exposure and risk can be denoted by $(p\|x)$ that indicates that the probability of cancer at time *t* is determined by the history of arsenic exposure *x* up to time *t*. The risk depends on exposure, or else, the history $\{y\}$ of inorganic arsenic in different organs. This situation can be diagrammed as $\{x\}\vec{}\,\{y\}\vec{}\,\{p\}$. This means $\{x\}$ determines$\{y\}$and $\{y\}$ determines $\{p\}$. Thus, the dose-time-response relation $(p\|x)$ may be written as by $(p\|x) = (p\|y) * (y\|x)$. The

$(y\|x)$ component corresponds to the relation of a PBPK model (mapping the exposure dose history $\{x\}$ into time courses $\{y\}$ of inorganic arsenic in different organs) and$(p\|y)$ represents an internal dose-response function. The general curve which better describes such relationship is in the form of Hill equation (Cox and Ricci, 1992):

$$P(y) = 1 - e^{(-by+cy^2+dy^3)} \quad (3)$$

where: *P(y)* = lifetime probability of the health effect, *y* = biologically effective dose of the toxicant at the target organ (internal dose), *b, c, d* = parameters calculated fitting a multistage model to the experimental dataset.

The most common way for calculating mortality (or any other toxic effect) through a dose-effect relationship, is to relate mortality to the pollutant concentration. The pathology model for arsenic uses two different equations for deriving the prevalence of fatal cancer within a given population. These include the Hill equation and an exponential equation (Ling and Liao, 2007) alternatively to the Hill equation:

$$P = 1 - \exp\left[-\left(a + b \cdot C_{H,i}^{C}\right)\right] \quad (4)$$ and,

$$P = \frac{P_{MAX} \times C_{H,i}^{n}}{EC_{50,i}^{n} + C_{H,i}^{n}} \quad (5)$$

Where: P = prevalence of the health effect, P_{MAX} = human maximum prevalence of those exposed to the contaminant, $C_{H,i}^{n}$= internal arsenic concentration in human target organ i (μg/g), $EC_{50,i}^{n}$ = 50% effect concentration (μg/g) of P_{MAX} for target organ, a, b, c = parameters calculated fitting a multistage model to the experimental dataset, n = Hill coefficient which is a measure of cooperativity, an n>1 represent a sublinear (sigmoidal) response indicating positive cooperatively, and n<1 represent a sub-linear response.

1.2.2 Area under the curve / slope factor association

1.2.2.1 General concept

Another way to associate internal dose with cancer health effects, is to use an established slope factor and to translate the intake based slope factor into a lifetime Area Under the Curve (AUC) related cancer potency factor, defined as AUC_{SF}. Hence, the respective cancer risk (R_C), will be estimated by multiplying the actual AUC_E for a given period of time as defined by the exposure scenario, with the related unit risk UR_{SF}, that results in risk associated to 10^{-6}.

$$R_C = \frac{AUC_E}{UR_{SF}} \cdot 10^{-6}$$

The area under the curve / slope factor (UR_{SF}) is defined as the AUC that results in risk associated to 10^{-6}. This in turn is derived as follow:

- Starting from the slope factor of the respective chemical, the chronic daily intake (CDI) that results in cancer risk equal to 10^{-6} is estimated. It has to be noted that this level of environmental risc is characterized as acceptable, hence, this intake levels is now defined as CDI_{AR}.
- The CDI_{AR} is used as an input to the respective PBPK model, and the AUC for a period of 70 years is estimated; the product of this computation, describes the AUC that corresponds to a risk of 10^{-6} and is defined as UR_{SF}, since it is originally based in the initial slope factor.

This method has clear advantages, since it allows us to incorporate all key parameters that induce inter-individual variability related to physiology (e.g. bodyweight, genetic polymorphism of enzymes associated with metabolism), as well as related to the exposure scenario, such as route dependent bioavailability differences. Moreover, considering that AUC is by definition the integral of internal exposure over time, the effect of highly dynamic exposure scenarios (including short term accidental events) to internal dose fluctuations are effectively captured and incorporated in the risk calculation. This is of particular importance for compounds that are not rapidly metabolized or eliminated, where short term exposure events result in long term internal exposure changes. Up to now, the method has been effectively applied in the case of dioxins release in an accidental fire of a plastic recycling plant (Sarigiannis, 2017).

It has to be noted that cancer risk estimates derived by this method are more conservative to the ones derived by original BBDR models. BBDR models translate human epidemiological data into micro relationships, associating them with internal dose; in contrast, the AUC/slope factor association method, starts from an animal based slope factor, which is already conservative in its nature.

1.2.2.2 Acrylonitrile

The quantitative estimates of risk from oral exposure and from inhalation exposure to acrylonitrile were determined. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day (U.S. EPA, 1987a). Three studies were used for the estimation of risk with regards to brain and spinal cord astrocytomas, Zymbal gland carcinomas and stomach papillomas/carcinomas (Biodynamics Inc., 1980a, b; Quast, 1980). Regarding oral exposure, the quantitative estimate was estimated as the geometric mean of three slope factors: 0.4 (Biodynamics Inc., 1980b), 0.4 (Biodynamics Inc., 1980a) and 0.99 per (mg/kg)/day (Quast, 1980). The overall risk of tumors was determined from the number of animals having tumors that were statistically significant at any site. The unit risk should not be used if the water concentration exceeds 600 ug/L, since above this concentration the unit risk may not be appropriate. Relatively large numbers of animals were treated and observed and a dose-response effect was observed in all studies. The slope factors derived from data on male rats (Biodynamics Inc., 1980a, b; Quast, 1980) were similar and within a factor of 3. The slope factors based on the three female rat studies (0.92, 0.37

and 0.29 per (mg/kg)/day) were similar to those of the respective male rat studies. In two of the studies (Biodynamics Inc., 1980a, b) the reported increases could vary considerably since interim necropsies were included with the final sacrifice. As for inhalation exposure, a cohort study of 1,345 male employees with potential for exposure to acrylonitrile analyzes cancer incidence and mortality from 1956 to 1976 was examined (O'Berg, 1980). The unit risk was calculated from a relative risk model adjusted for smoking and based on a continuous lifetime equivalent of occupational exposure. An exposure of 15 ppm was assumed to be the 8-hour TWA with an average exposure duration of 9 years. The maximum possible age at the end of the observation period was assumed to be 60 years. The cohort was sufficiently large and was followed for an adequate time period. A dose-response relationship was seen for the increased cancer risk. The increased risk remained after adjustment for smoking. Finally, the inhalation slope factor of 0.24 (mg/kg/day)-1 was used for estimating the respective UR_{SF}. This corresponds to a CDI_{AR} of 0.0042 µg/kg_bw/d, which in turn is translated in an UR_{SF} of 0.00082 µg*h/L. To estimate the cancer risks associated with acrylonitrile exposure, the lifetime internal exposure levels presented in Report DC2 were used.

1.2.2.3 Cadmium

The quantitative estimates of risk from oral exposure and from inhalation exposure to cadmium were determined. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day (U.S. EPA, 1987b). Since, there are no positive studies of orally ingested cadmium suitable for quantification, the quantitative estimate of carcinogenic risk from inhalation exposure was only considered. A mortality study of 292 cadmium production workers employed for a minimum of 2 years was used for estimating risks regarding respiratory and prostate cancer (Thun et al., 1985). To examine further the mortality experience of these workers, investigators from the National Institute for Occupational Safety and Health extended the study to include 602 white males with at least 6 months of production work in the same plant between 1940 and 1969. Vital status was determined through 1978, which included the addition of 5 years to the original follow-up. The unit risk should not be used if the air concentration exceeds 6 ug/m^3, since above this concentration the unit risk may not be appropriate. The data were derived from a relatively large cohort. Effects of arsenic and smoking were accounted for in the quantitative analysis for cadmium effects. It was considered that the use of available human data was reliable because of species variations in response and the type of exposure (cadmium salt vs. cadmium fume and cadmium oxide).

For cadmium, the slope factor of 6.3 $(mg/kg/day)^{-1}$ was used for estimating the respective UR_{SF}. As a result, the respective CDI_{AR} was equal to 0.00016 µg/kg_bw/d, that was translated in an URSF of 0.18 µg*h/L. To estimate the cancer risks associated with cadmium exposure, the lifetime internal exposure levels presented in Report DC2 were used.

2 LONG-TERM HEALTH EFFECT ESTIMATES RELATED TO THE ACCIDENTAL SCENARIOS DESCRIBED IN PEC CASE STUDIES

2.1 Benzene related cancer risk

The cancer risks associated with benzene exposure for the different scenarios are described below, while the detailed impacts are presented in Tables 4-1 to 4-9.

2.1.1 Primary Fractionator – Gas Phase

In this plant item, the benzene in gaseous phase is stored in combination with other gases representing 10% in volume of the overall mixture. This is the scenario with the highest (5.2E-02 and 2.6E-02 for winter and summer respectively) expected impacts (Table 4-1), as a result of the highest amount of gaseous releases, which in turn results in significant levels of contamination for a large distance from the source. The impacts are higher in winter, as a result of the lower mixing height, that favours pollutant accumulation.

2.1.2 Virgin Naphtha Storage Tanks - Liquid Phase

This section describes health effects that could be observed in workers present in Plant A due to catastrophic damage of the Virgin Naphtha Storage Tank and consequent instantaneous release of all the benzene in liquid phase stored in the item. Accidental events related to this component results to limited impacts to workers in the range of 9.5E-03 and 6.8E-03 for winter and summer respectively (Table 4-2).

2.1.3 Primary Fractionator Storage Tanks – Liquid Phase

Tables A4 and A5 show the health effects that could be observed in workers following damage of the primary fractionator of Plant A resulting in instantaneous release of all the benzene in liquid phase stored in the item. This incidental event would result in the highest impacts among the scenarios involving worker scenarios, in the range of 9.9E-03 and 4.6E-03 (Table 4-2).

2.1.4 Quench Column Tank – Liquid Phase

In this scenario, it is assumed that catastrophic damage of the Quench Column Tank in Plant A will cause instantaneous release of all the benzene in liquid phase stored in the item. This will result in a moderate contamination of the surrounding area, which is also reflected in the expected impacts which equals to 1.3E-4 for summer and 8.1E-04 in the winter (Table 4-2).

2.1.5 Heavy Gasoline Stripper – Liquid Phase

Accidental damage of the heavy gasoline stripper tank results in instantaneous release of all the benzene in liquid phase stored in item. This will result in risks related to worker exposure, in the range of 4.3E-03 and 3.7E-04 (Table 4-2).

2.1.6 Heavy Gasoline Stripper – Gas Phase

Catastrophic damage of the Heavy Gasoline Stripper of Plant A would cause instantaneous release of all the benzene in gaseous phase stored in the item. The entire amount of benzene in gaseous phase would be released into the environment from the pressurized heavy gasoline stripper tank in 1 minute with a release rate of 439 g/s. However, this incidental event will result in lower impacts compared with the previous scenarios, in the range of 9.5E-03 and 6.8E-03 for winter and summer respectively for adults and 2.9E-03 and 1.1E-03 for winter and summer respectively for children (Table 4-3).

2.1.7 Debutanizer – Gas Phase

Damage of the Debutanizer of Plant A will cause instantaneous release of all the benzene in gaseous phase stored in the item. Among the individual catastrophic scenarios, this is the one with the highest impact, at the level of 2.9E-02 for winter and 1.2E-02 for the summer (Table 4-4). The significantly higher impact in the winter is the result of the meteorological conditions, that do not favour the dispersion of the contaminant, resulting in elevated concentrations for a large amount of population. It is also remarkable that in the case of a wintertime accidental event, 14 children will experience risk 10 times higher than the accepted risk of 10^{-6}.

2.1.8 Debutanizer – Liquid Phase

In this incident scenario, the catastrophic damage of the Debutanizer tank of Plant A causes instantaneous release of all the benzene in liquid phase stored in the item. Among the individual catastrophic scenarios, this is the one with the second highest impact (following the gaseous releases of debutanizer catastrophic event), in at the level of 1.7E-02 for winter and 1.2E-02 for the summer (Table 4-5). Compared to the gaseous releases of debutanizer catastrophic event, the difference in the process is also reflected in the differences in the impact between summer and winter. In practice, the higher temperatures in the summer, favour the higher evaporation rate of the liquid, resulting in elevated concentrations close to the release source, which is reflected in the highest impact for workers. In contrast, during the winter season, the meteorology does not favour pollutant dispersion in long distance, thus resulting in higher exposure levels, that are also reflected in the calculated risk.

2.1.9 Cracking Gasoline Tank - liquid phase

“Cracking Gasoline Tank”, liquid phase results in impacts of 9.5E-03 and 6.8E-03 for winter and summer respectively for adults and 2.9E-03 and 1.1E-03 for winter and summer respectively for children (Table 4-6). Similarly to previous cases, the accidental process related to gaseous releases results in the highest impact during winter, while the liquid one during summer.

2.1.10 Other Items - Liquid Phase

Calculations of the health impacts due to accidental damage of the other items present in Plant A indicate toxicological changes comparable or less severe than those described above for the Quench Column Tank. This would be observed in both the summer and winter season scenarios. The accidental scenarios associated with "Quench Column Tank", "Cracking Gasoline Unit Buffer Tank", "Cracking Gasoline Tank 2" result in the lowest contamination of the surrounding area and the respective impact, in the range of 2.2 to 4.7E-04 cases (Table 4-6).

2.1.11 Simultaneous Damage of the Items "Virgin Naphtha Storage Tanks", "Cracking Gasoline Buffer Tanks", and "Cracking Gasoline Tank" - Liquid Phase

Although this scenario (Table 4-8) includes a combination of three type of damages, the involved processes do not result in intense releases that could elevate benzene levels for a large area. Thus, the expected impacts account for 3.4E-03 cases in winter and 1.73E-03 summer respectively.

2.1.12 Simultaneous Damage of the Items "Primary Fractionator", "Heavy Gasoline Stripper", and "Debutanizer" – Gas Phase

This accidental scenario (Table 4-9) that includes the simultaneous damage of 3 main components of Plant A is expected to result in the highest impacts. Considering that in this case, all the releases are in the gaseous phase, a large part of the population living in the area will experience exposure to very high concentrations. This is even more evident in the winter, where the meteorological conditions do not favour dispersion. As a result, the health impact levels of a winter accidental event would result in 6.8E-0.2 cases including all population groups (workers, adults, elderly and children). It has also to be noted that almost 85 children will experience a lifetime risk above 10^{-5}, which is one order of magnitude higher than the one considered as acceptable for environmental hazards.

2.2 Acrylonitrile related cancer risk

The scenarios related to acrylonitrile long term health (cancer) effects are given below. Details on the estimated impacts and the affected population are presented in Tables 4-10 to 4.15.

2.2.1 Acrylonitrile Storage Tank

In this incident scenario (Table 4-10), the catastrophic damage of the Acrylonitrile Storage Tank in Plant A is assumed to cause instantaneous release of all the acrylonitrile in liquid phase stored in the item. In this scenario, the highest amount of acrylonitrile is released, resulting in significant impacts of population to be exposed to the airborne acrylonitrile. It has to be noted, that acrylonitrile is highly volatile and upon released, it is rapidly evaporating into the gaseous phase, while distribution to other

media in negligible. This scenario will result in impact in the range of 2.9E-02 and 2.2E-02 for winter and summer respectively for adults, and 3.7E-03 and 2.6E-03 for winter and summer respectively for children.

2.2.2 Unit Buffer Vessel

This section describes health effects that are likely to be observed in workers present in Plant A as a consequence of catastrophic damage of the Unit Buffer Vessel and consequent instantaneous release of all the acrylonitrile in liquid phase stored in the item (Table 4-11). This scenario will result in impact in the range of 2.3E-02 and 1.7E-02 for winter and summer respectively for adults, and 3.1E-03 and 2.2E-03 for winter and summer respectively for children.

2.2.3 Elastomer Production Reactor

Catastrophic damage of the Elastomer Production Reactor of Plant A would cause instantaneous release of all the acrylonitrile in liquid phase stored in the item. The estimated health impacts on workers present in Plant A for an incident occurring in winter or during the summer season are reported in Table 4-12. Among the various scenarios involving acrylonitrile, this is the one with the highest reported impacts, in the range of 1.3E-01 and 7.0E-02 for winter and summer respectively for adults, and 1.5E-02 and 1.1E-03 for winter and summer respectively for children.

2.2.4 Stripping Column

In this simulated incident (Table 4-13), it is assumed that catastrophic damage of the Stripping Column in Plant A causes instantaneous release of all the acrylonitrile in liquid phase stored in the item. This scenario will result in impact in the range of 2.3E-02 and 1.8E-02 for winter and summer respectively for adults, and 3.3E-03 and 2.4E-03 for winter and summer respectively for children.

2.2.5 Simultaneous Damage of the Items "Acrylonitrile Storage Tank", "Unit Buffer Vessel", and "Stripping Column"

In this simulated event (Table 4-14), the simultaneous release of acrylonitrile storage tank, unit buffer vessel, and stripping column was investigated. The expected health impacts are the result of the contribution of the releases from all related processes, thus, in the range of 3.9E-02 and 3.1E-02 for winter and summer respectively for adults, and 4.3E-03 and 3.0E-03 for winter and summer respectively for children.

2.2.6 Simultaneous Damage of the Items "Acrylonitrile Storage Tank", "Unit Buffer Vessel", and "Elastomer Production Reactor"

In this simulated event (Table 4-15), the simultaneous release of acrylonitrile storage tank, unit buffer vessel, and elastomer production reactor. In contrast to the previous simultaneous scenario, the

expected health impacts are governed by the releases from elastomer production reactor, thus, in the range of 1.3E-01 and 6.5E-02 for winter and summer respectively for adults, and 1.5E-02 and 1.1E-03 for winter and summer respectively for children.

2.3 Arsenic related cancer risk

The cancer risks associated with benzene exposure for the different scenarios are described below. Details on the estimated risk and the amount of population subjected to the risk are given in tables 4-16 to 4-18.

2.3.1 Pregant solution tank

In this incident scenario, the catastrophic damage of the Pregant solution tank in Plant B is assumed to cause instantaneous release of all the arsenic in liquid phase stored in the item. Among the catastrophic scenarios in Plant B, this is the one that results in the highest impacts, since a larger fraction of the population is exposed to high levels of airborne arsenic, as a result of the large amount of arsenic released after the catastrophic rupture. It has to be noted, that due to its high vapor pressure, arsenic in rapidly moving from the liquid phase to the airborne one. However, some very small amounts of arsenic will also be adsorbed in particles and settled house dust of the people living in the area, but the contribution of these exposure pathways is several orders of magnitude (6 to 7) lower than inhalation. Due to the high toxic potency of arsenic, the estimated risks are in the order of 10^{-4} to 10^{-3}, thus, resulting in an increase of 20 to 90% of the existing background risk of associated to the environmentally relevant exposure (from all sources and pathways) risks of arsenic. With regard to seasonal differences of a potential incident, similarly to benzene and acrylonitrile, higher concentrations are expected during winter time, as a result of the lower mixing height that favours airborne pollutant accumulation. It has also to be noted, that gender differences in susceptibility to arsenic exposure have been accounted for, and assuming the cumulative risk for all cancer types related to arsenic exposure, males are subjected to an almost 20% higher risk than women. Children, similarly to the rest of the catastrophic scenarios investigated in Plant A, are subjected to a higher lifetime risk of almost 80%. These gender and age dependent differences, are relevant for all arsenic related catastrophic scenarios presented below.

2.3.2 Leach thickener

This section describes health effects that are likely to be observed for the workers and the population living close to Plant B, as a consequence of catastrophic damage of the Leach Thickener and the consequent instantaneous release of all the arsenic in liquid phase stored in the item. The pattern of the distribution of arsenic among the various environmental phases will be similar to the Pregant solution tank, however, due to the significantly lower amount of arsenic released, a smaller amount of the population will be subjected to risks that are above (2 to 10%) the arsenic background risk levels.

2.3.3 High shear pre-oxidation, Cyanide leach circuit, Cyanide destruction and Strip circuit

In all these catastrophic ruptures, the same amount of arsenic is released in the environment, thus, similar levels of airborne contamination and intake levels are expected, which are however, in the same magnitude of order to the ones of the leach thickener, thus, increasing the risks associated to environmental background arsenic exposure by 1 to 5%.

2.4 Cadmium related cancer risk

For all the three relevant scenario of accidental releases, namely cadmium leaching reactors, filter press and precipitation tank, estimated lifetime cancer risks are far below (7 to 8) magnitude of orders below the levels considered as acceptable (10^{-6}). This is the result of the extremely low vapour pressure of cadmium that does not favour airborne dispersion. On the other hand, considering that cadmium is released in industrial soil, this is not going to be mobilised through the food chain, thus, not contributing to dietary ingestion pathways. The only possible mechanism of exposure is the non-dietary ingestion of very small amount of soil of people living nearby, which is very low, thus limiting uptake of cadmium to the range of 10^{-10}, which results in the negligible cancer risk and the respective health impact mentioned above. In the case that the estimated risks were not negligible, it has to be mentioned that females would experience almost 60% higher risk compared to males, due to higher lifetime internal dose, which is the result of the lower renal excretion in females.

3 CONCLUSIONS

- Gaseous emissions show the highest impacts during the winter season while liquid emissions show higher impacts during the summer. This behavior can be explained considering that during the cold season the mixing height is lower resulting in higher toxic concentration levels, while in the summer the higher temperatures favor evaporation, resulting in higher airborne releases. This is the case for all compounds characterized by high vapor pressure included in the analysis (benzene, acrylonitrile and arsenic), but not for cadmium.

- Risks associated to arsenic and the related health impacts are the highest ones, as the result of the very high toxic potency. The long-term health effects of the various site-specific cancers, are expected to derive the highest health impacts among the various scenarios investigated in PEC.
- Cancer risks associated with arsenic are differentiated within genders; overall, males are subjected to an almost 20% higher risk compered to women, due to differences in metabolism and response to arsenic metabolites.
- Risk and the associated health impact of cadmium are practically negligible. This is the result of the very low vapor pressure that does not favor the distribution and transportation in airborne media. Potential uptake related to cadmium release is associated only with non-dietary ingestion of soil, excluding any other inhalation, dermal or dietary ingestion pathway.
- It has to be noted, that the health risks associated with an accidental event in some cases exceed the background environmental risks of the involved compounds. This shows that short term exposure events of none persisting compounds resulting from accidents or malicious actions, are able to pose significant long term health risks.
- It worth to be highlighted that the lifetime cancer risks of the children is more than 70% higher compared to the one of adults exposed to the same levels of contamination, as a result of the highest bodyweight normalized inhalation rate which in turn results in higher uptake and internal dose of the toxic compounds and their metabolites.
- It is very useful to have the actual background exposure levels of the population to these compounds through human biomonitoring data. In the absence of HBM data (and the proper computational tools for back calculating daily uptake), conservative bottom up approaches are used for estimating the background environmental risk, thus, usually overestimating background exposure. In this case, the relative importance of long term health effects associated with the catastrophic incidences are usually underestimated.
- The overall exposure and risk assessment of releases of compounds with different physico-chemical and toxicokinetic properties is greatly facilitated by the use of integrated exposure computational platforms, able to capture the dynamics of environmental fate, the contribution

of the relevant exposure pathways and the respective lifetime internal dose, accounting as well for age and gender related differences.

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4 ANNEX

4.1 Benzene health impact assessment

Table 4-1. Health Impact of the Simulated Incident for the Population Exposed to Benzene Following Damage of the Item "Primary Fractionator", gas phase, in Plant A.

Concentration (ppm)	Leukemia risk (adults)	Winter			Summer			Leukemia risk (children)	Winter	Summer
		Workers	Adults	Elderly (> 65 years)	Workers	Adults	Elderly (> 65 years)		Children (< 18 years)	Children (< 18 years)
0.1-1	1.1E-06	20 M 5 F	2,219 M 2,404 F	648 M 703 F	23 M 5F	3,139 M 3,401 F	917 M 994 F	1.8E-06	546 M 592 F	773 M 837 F
1-2.5	1.2E-06	9 M 2 F	2,530 M 1,658 F	648 M 447 F	11 M 3 F	800 M 867 F	234 M 253 F	2.1E-06	546 M 592 F	197 M 213 F
2.5-5	1.5E-06	8 M 2 F	799 M 866 F	233 M 253 F	10 M 2 F	276 M 299 F	80 M 87 F	2.6E-06	197 M 213 F	68 M 73 F
5-10	2.0E-06	9 M 2 F	446 M 483 F	130 M 141 F	11 M 3 F	141 M 153 F	41 M 44 F	3.4E-06	110 M 119 F	35 M 37 F
10-25	3.3E-06	14 M 3 F	276 M 299 F	80 M 87 F	19 M 5 F	85 M 92 F	25 M 27 F	5.7E-06	68 M 73 F	21 M 23 F
25-52	6.0E-06	14 M 3 F	97 M 105 F	28 M 31 F	22 M 5 F	27 M 30 F	8 M 9 F	1.0E-05	24 M 26 F	7 M 7 F
52-100	1.1E-05	15 M 4 F	43 M 46 F	12 M 13 F	41 M 10 F	6 M 7 F	2 M 2 F	1.9E-05	10 M 11 F	1 M 2 F
100-300	2.8E-05	29 M 12 F	24 M 26 F	7 M 8 F	54 M 13 F			4.7E-05	6 M 6 F	
300-800	7.4E-05	54 M 13 F			17 M 5 F					
800-1,000	1.2E-04	7 M 2 F			2 M 1 F					
1,000-4,000	3.4E-04	21 M 5 F			6 M 2 F					
> 4,000	1.2E-03	7 M 1 F			2 M 1 F					
Health Impact		**5.2E-02**			**2.6E-02**				**8.5E-03**	**4.8E-03**

Table 4-2. Health Impact of the Simulated Incident in Workers Exposed to Benzene Following Damage of the Items "Virgin Naphtha Storage Tanks", "Heavy Gasoline Stripper", "Quench Column Tank" and "Primary Fractionator", liquid phase, Plant A.

Concentration (ppm)	Leukemia risk (adults)	"Virgin Naphtha Storage Tanks", liquid phase		"Heavy Gasoline Stripper", liquid phase		"Quench Column Tank", liquid phase		"Primary Fractionator", liquid phase	
		Winter	Summer	Winter	Summer	Winter	Summer	Winter	Summer
0.1-1	1.1E-06	35 M 9 F	55 M 14 F	20 M 5 F	38 M 10 F	29 M 7 F	30 M 8 F	27 M 7 F	26 M 6 F
1-2.5	1.2E-06	44 M 10 F	64 M 16 F	10 M 3 F	33 M 8 F	18 M 4 F	21 M 5F	14 M 4 F	14 M 3 F
2.5-5	1.5E-06	23 M 5 F	29 M 7 F	10 M 2 F	38 M 9 F	20 M 5 F	23 M 6 F	13 M 3 F	12 M 4 F
5-10	2.0E-06	12 M 4 F	15 M 4 F	12 M 3 F	22 M 5 F	29 M 7 F	33 M 8 F	15 M 4 F	16 M 4 F
10-25	3.3E-06	7 M 2 F	9 M 2 F	19 M 5 F	13 M 3 F	34 M 8 F	24 M 6F	30 M 7 F	33 M 8 F
25-52	6.0E-06	2 M 1 F	3 M 2 F	18 M 5 F	5 M 1 F	12 M 3 F	9 M 2 F	53 M 13 F	51 M 13 F
52-100	1.1E-05	1 M 0 F	2 M 1 F	23 M 6 F	2 M 0 F	5 M 1 F	4 M 1 F	34 M 9 F	25 M 6 F
100-300	2.8E-05	0 M 0 F	1 M 0 F	20 M 5 F	1 M 0 F	4 M 1 F	3 M 1 F	26 M 6 F	19 M 5 F
300-800	7.4E-05	0 M 0 F	0 M 0 F	6 M 2 F		1 M 0 F	1 M 0 F	68 M 2 F	6 M 2 F
800-1,000	1.2E-04	0 M 0 F	0 M 0 F	1 M 0 F				1 M 0 F	1 M 0 F
1,000-4,000	3.4E-04	0 M 0 F	0 M 0 F	2 M 1 F				3 M 1 F	2 M 1 F
> 4,000	1.2E-03	0 M 0 F	0 M 0 F	1 M 0 F				1 M 0 F	1 M 0 F
Health Impact		**6.9E-03**	**2.7E-03**	**4.3E-03**	**4.1E-03**	**6.8E-04**	**6.0E-04**	**9.9E-03**	**4.6E-03**

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Table 4-3. Health Impact of the Simulated Incident for the Population Exposed to Benzene Following Damage to the Item "Heavy Gasoline Stripper", gas phase, in Plant A.

Concentration (ppm)	Leukemia risk (adults)	Winter			Summer			Leukemia risk (children)	Winter	Summer
		Workers	Adults	Elderly (> 65 years)	Workers	Adults	Elderly (> 65 years)		Children (< 18 years)	Children (< 18 years)
0.1-1	1.1E-06	22 M 6 F	2,567 M 2,781 F	750 M 813 F	28 M 7 F	1,052 M 1,140 F	307 M 333 F	1.8E-06	632 M 684 F	259 M 280 F
1-2.5	1.2E-06	12 M 3 F	238 M 258 F	69 M 75 F	17 M 4 F	73 M 80 F	25 M 23 F	2.1E-06	58 M 65 F	18 M 19 F
2.5-5	1.5E-06	11 M 3 F	81 M 88 F	23 M 25 F	18 M 5 F	23 M 25 F	6 M 7 F	2.6E-06	20 M 21 F	5 M 6 F
5-10	2.0E-06	14 M 4 F	40 M 43 F	11 M 12 F	32 M 8 F	7 M 8 F	2 M 2 F	3.4E-06	10 M 10 F	2 M 2 F
10-25	3.3E-06	31 M 8 F	20 M 22 F	6 M 6 F	42 M 10 F			5.7E-06	5 M 5 F	
25-52	6.0E-06	41 M 10 F	1 M 1 F	1 M 1 F	15 M 4 F			1.0E-05		
52-100	1.1E-05	22 M 5 F			7 M 2 F			1.9E-05		
100-300	2.8E-05	16 M 4 F			5 M 1 F			4.7E-05		
300-800	7.4E-05	5 M 1 F			2 M 0 F					
800-1,000	1.2E-04	1M 0 F								
1,000-4,000	3.4E-04	2 M 0 F								
> 4,000	1.2E-03	1 M 0 F								
Health Impact		**9.5E-03**			**6.8E-03**				**2.9E-03**	**1.1E-03**

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Table 4-4. Health Impact of the Simulated Incident for the Population Exposed to Benzene Following Damage to the Item "Debutanizer", gas phase, in Plant A.

Concentration (ppm)	Leukemia risk (adults)	Winter			Summer			Leukemia risk (children)	Winter	Summer
		Workers	Adults	Elderly (> 65 years)	Workers	Adults	Elderly (> 65 years)		Children (< 18 years)	Children (< 18 years)
0.1-1	1.1E-06	16 M 4 F	3,056 M 3,310 F	893 M 967 F	19 M 5 F	2,412 M 2,613 F	705 M 764 F	1.8E-06	752 M 815 F	593 M 643 F
1-2.5	1.2E-06	8 M 2 F	694 M 752 F	203 M 220 F	10 M 3 F	221 M 239 F	64 M 70 F	2.1E-06	171 M 185 F	54 M 59 F
2.5-5	1.5E-06	7 M 2 F	239 M 259 F	70 M 76 F	10 M 2 F	75 M 81 F	22 M 24 F	2.6E-06	59 M 64 F	18 M 20 F
5-10	2.0E-06	9 M 3 F	122 M 133 F	36 M 39 F	13 M 3 F	37 M 40 F	11 M 12 F	3.4E-06	30 M 32 F	9 M 10 F
10-25	3.3E-06	14 M 4 F	74 M 80 F	22 M 23 F	20 M 5 F	21 M 22 F	6 M 7 F	5.7E-06	18 M 20 F	5 M 5 F
25-52	6.0E-06	15 M 4 F	25 M 27 F	7 M 8 F	22 M 5 F	4 M 5 F	1 M 1 F	1.0E-05	6 M 6 F	1 M 1 F
52-100	1.1E-05	15 M 4 F	9 M 10 F	3 M 3 F	20 M 5 F			1.9E-05	2 M 2 F	
100-300	2.8E-05	35 M 9 F	2 M 3 F	1 M 1 F	15 M 4 F			4.7E-05		
300-800	7.4E-05	15 M 4 F			54M 1 F					
800-1,000	1.2E-04	2 M 0 F								
1,000-4,000	3.4E-04	6 M 1 F			2 M 0 F					
> 4,000	1.2E-03	1 M 0 F			1 M 0 F					
Health Impact		**2.4E-02**			**9.5E-03**				**4.5E-03**	**2.7E-03**

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Table 4-5. Health Impact of the Simulated Incident for the Population Exposed to Benzene Following Damage to the Item "Debutanizer", liquid phase, in Plant A.

Concentration (ppm)	Leukemia risk (adults)	Winter			Summer			Leukemia risk (children)	Winter	Summer
		Workers	Adults	Elderly (> 65 years)	Workers	Adults	Elderly (> 65 years)		Children (< 18 years)	Children (< 18 years)
0.1-1	1.1E-06	20 M 5 F	2,781 M 3,013 F	813 M 881 F	22 M 5 F	2,384 M 2,583 F	697 M 755 F	1.8E-06	685 M 742 F	587 M 635 F
1-2.5	1.2E-06	10 M 3 F	299 M 324 F	87 M 95 F	12 M 5 F	217 M 235 F	64 M 69 F	2.1E-06	74 M 80 F	53 M 58 F
2.5-5	1.5E-06	10 M 2 F	102 M 111 F	30 M 32 F	11 M 5 F	74 M 80 F	22 M 23 F	2.6E-06	25 M 27 F	18 M 20 F
5-10	2.0E-06	12 M 3 F	52 M 56 F	15 M 16 F	14 M 5 F	36 M 40 F	11 M 11 F	3.4E-06	13 M 14 F	9 M 10 F
10-25	3.3E-06	19 M 5 F	30 M 32 F	9 M 9 F	17 M 4 F	24 M 22 F	6 M 6 F	5.7E-06	7 M 8 F	5 M 5 F
25-52	6.0E-06	18 M 5 F	8 M 9 F	2 M 3 F	18 M 2 F	4 M 5 F	1 M 2 F	1.0E-05	2 M 2 F	1 M 1 F
52-100	1.1E-05	23 M 6 F	1 M 1 F		23 M 5 F			1.9E-05		
100-300	2.8E-05	20 M 5 F			18 M 5 F			4.7E-05		
300-800	7.4E-05	6 M 2 F			5 M 2 F					
800-1,000	1.2E-04	1 M 0 F			1 M 0 F					
1,000-4,000	3.4E-04	2 M 1 F			2 M 1 F					
> 4,000	1.2E-03	1 M 0 F			1 M 0 F					
Health Impact		**1.4E-02**			**8.9E-03**				**3.2E-03**	**2.7E-03**

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Table 4-6. Health Impact of the Simulated Incident for the Population Exposed to Benzene Following Damage to the Item "Cracking Gasoline Tank", liquid phase, in Plant A

Concentration (ppm)	Leukemia risk (adults)	Winter			Summer			Leukemia risk (children)	Winter	Summer
		Workers	Adults	Elderly (> 65 years)	Workers	Adults	Elderly (> 65 years)		Children (< 18 years)	Children (< 18 years)
0.1-1	1.1E-06	77 M 20 F	283 M 307 F	83 M 89 F	92 M 23 F	218 M 236 F	64 M 69 F	1.8E-06	70 M 75 F	54 M 58 F
1-2.5	1.2E-06	81 M 20 F	5 M 5 F	2 M 2 F	78 M 20 F	1 M 1 F		2.1E-06	1 M 1 F	
2.5-5	1.5E-06	36 M 10 F			29 M 7 F			2.6E-06		
5-10	2.0E-06	19 M 5 F			15 M 4 F			3.4E-06		
10-25	3.3E-06	12M 3F			9 M 2 F			5.7E-06		
25-52	6.0E-06	4 M 1 F			3 M 1 F			1.0E-05		
52-100	1.1E-05	2 M 0 F			2 M 0 F			1.9E-05		
100-300	2.8E-05	1 M 0 F			1 M 0 F			4.7E-05		
300-800	7.4E-05	0 M 0 F								
800-1,000	1.2E-04	0 M 0 F								
1,000-4,000	3.4E-04	0 M 0 F								
> 4,000	1.2E-03	0 M 0 F								
Health Impact		**7.9E-03**			1.1E-03				**2.7E-04**	**2.0E-04**

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Table 4-7. Health Impact of the Simulated Incident in Workers Exposed to Benzene Following Damage of the Items "Cracking Gasoline Unit Buffer Tank", "Cracking Gasoline Tank" and "Cracking Gasoline Tank 2", liquid phase, Plant A

Concentration (ppm)	Leukemia risk (adults)	"Cracking Gasoline Unit Buffer Tank", liquid phase		"Cracking Gasoline Tank", liquid phase		"Cracking Gasoline Tank 2", liquid phase	
		Winter	Summer	Winter	Summer	Winter	Summer
0.1-1	1.1E-06	28 M 7 F	30 M 7 F	77 M 20 F	92 M 23 F	69M 17 F	80 M 20 F
1-2.5	1.2E-06	14 M 3 F	15 M 3 F	81 M 20 F	78 M 20 F	61 M 15 F	67 M 16 F
2.5-5	1.5E-06	12 M 3 F	16 M 4 F	36 M 10 F	29 M 7 F	42 M 10 F	30 M 8 F
5-10	2.0E-06	18 M 4 F	14 M 3 F	19 M 5 F	15 M 4 F	22 M 5 F	16 M 4 F
10-25	3.3E-06	13 M 3 F	8 M 2 F	12M 3F	9 M 2 F	13 M 3 F	10 M 2 F
25-52	6.0E-06	4 M 1 F	3 M 1 F	4 M 1 F	3 M 1 F	5 M 1 F	3 M 1 F
52-100	1.1E-05	2 M 0 F	1 M 0 F	2 M 0 F	2 M 0 F	2 M 0 F	1 M 0 F
100-300	2.8E-05	1 M 0 F	1 M 0 F	1 M 0 F	1 M 0 F	1 M 0 F	1 M 0 F
300-800	7.4E-05						
800-1,000	1.2E-04						
1,000-4,000	3.4E-04						
> 4,000	1.2E-03						
Health Impact		**2.6E-04**	**2.2E-04**	**4.7E-04**	**4.5E-04**	**4.6E-04**	**4.1E-04**

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Table 4-8. Health Impact of the Simulated Incident for the Population Exposed to Benzene Following Simultaneous Damage of the Items "Virgin Naphtha Storage Tanks", "Cracking Gasoline Buffer Tanks", and "Cracking Gasoline Tank" (all liquid phase), in Plant A

Concentration (ppm)	Leukemia risk (adults)	Winter			Summer			Leukemia risk (children)	Winter	Summer
		Workers	Adults	Elderly (> 65 years)	Workers	Adults	Elderly (> 65 years)		Children (< 18 years)	Children (< 18 years)
0.1-1	1.1E-06	35 M 9 F	408 M 442 F	119 M 129 F	39 M 10 F	294 M 318 F	86 M 93 F	1.8E-06	100 M 109 F	72 M 78 F
1-2.5	1.2E-06	41 M 10 F	29 M 31 F	8 M 9 F	64 M 16 F	17 M 18 F	5 M 3 F	2.1E-06	7 M 8 F	4 M 4 F
2.5-5	1.5E-06	59 M 15 F	8 M 7 F	2 M 2 F	59 M 15 F	2 M 1 F	1 M 1 F	2.6E-06	2 M 2 F	1 M 1 F
5-10	2.0E-06	43 M 11 F	1 M 1 F		43 M 11 F			3.4E-06		
10-25	3.3E-06	56 M 14 F			29 M 7 F			5.7E-06		
25-52	6.0E-06	39 M 10 F			9 M 2 F			1.0E-05		
52-100	1.1E-05	13 M 3 F			4 M 1 F			1.9E-05		
100-300	2.8E-05	6 M 1 F			3 M 0 F			4.7E-05		
300-800	7.4E-05	4 M 1 F			1 M 0 F					
800-1,000	1.2E-04	1 M 0 F								
1,000-4,000	3.4E-04									
> 4,000	1.2E-03									
Health Impact		**3.0E-03**			**1.7E-03**				**4.2E-04**	**2.9E-04**

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Table 4-9. Health Impact of the Simulated Incident for the Population Exposed to Benzene Following Simultaneous Damage of the Items "Primary Fractionator", "Heavy Gasoline Stripper", and "Debutanizer" (all gas phase), in Plant A

Concentration (ppm)	Leukemia risk (adults)	Winter			Summer			Leukemia risk (children)	Winter	Summer
		Workers	Adults	Elderly (> 65 years)	Workers	Adults	Elderly (> 65 years)		Children (< 18 years)	Children (< 18 years)
0.1-1	1.1E-06	15 M 4 F	2,219 M 2,403 F	649 M 703 F	4 M 1 F	3,139 M 3,401 F	918 M 994 F	1.8E-06	546 M 592 F	773 M 837 F
1-2.5	1.2E-06	7 M 2 F	1,531 M 1,658 F	447 M 485 F	9 M 2 F	801 M 867 F	234 M 254 F	2.1E-06	377 M 408 F	197 M 213 F
2.5-5	1.5E-06	6 M 2 F	792 M 858 F	231 M 251 F	8 M 2 F	270 M 293 F	79 M 86 F	2.6E-06	195 M 211 F	66 M 73 F
5-10	2.0E-06	7 M 2 F	447 M 485 F	131 M 142 F	9 M 2 F	143 M 155 F	42 M 45 F	3.4E-06	110 M 119 F	35 M 38 F
10-25	3.3E-06	11 M 3 F	283 M 307 F	83 M 90 F	16 M 4 F	92 M 99 F	27 M 29 F	5.7E-06	70 M 76 F	23 M 24 F
25-52	6.0E-06	11 M 3 F	94 M 102 F	27 M 30 F	19 M 5 F	27 M 29 F	8 M 8 F	1.0E-05	23 M 25 F	7 M 7 F
52-100	1.1E-05	13 M 3 F	46 M 50 F	14 M 15 F	42 M 11 F	8 M 9 F	2 M 3 F	1.9E-05	11 M 12 F	2 M 2 F
100-300	2.8E-05	53 M 13 F	28 M 30 F	8 M 9 F	72 M 18 F			4.7E-05	7 M 7 F	
300-800	7.4E-05	67 M 17 F			23 M 6 F					
800-1,000	1.2E-04	8 M 2 F			2 M 1 F					
1,000-4,000	3.4E-04	29 M 7 F			9 M 2 F					
> 4,000	1.2E-03	9 M 2 F			3 M 1 F					
Health Impact		**6.0E-02**			**3.0E-02**				**7.9E-03**	**4.9E-03**

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4.2 Acrylonitrile

Table 4-10. Health Impact of the Simulated Incident for the Population Exposed to Acrylonitrile Following Damage of the Item "Acrylonitrile Storage Tank", in Plant A

Concentration (ppm)	Cancer risk (adults)	Winter			Summer			Cancer risk (children)	Winter	Summer
		Workers	Adults	Elderly (> 65 years)	Workers	Adults	Elderly (> 65 years)		Children (< 18 years)	Children (< 18 years)
0.1-1	2.6E-05	67 M 17 F	253 M 274 F	80 M 80 F	74 M 19 F	179 M 194 F	52 M 57 F	2.8E-05	62 M 67 F	44 M 48 F
1-2.5	3.1E-05	48 M 12 F	9 M 10 F	3 M 3 F	52 M 13 F	3 M 4 F	1 M 1 F	3.3E-05	2 M 2 F	1 M 1 F
2.5-5	4.0E-05	33 M 8 F			24 M 6 F			4.1E-05		
5-10	5.5E-05	17 M 4 F			12 M 3 F			5.8E-05		
10-25	9.7E-05	10 M 3 F			7 M 2 F			1.0E-04		
25-52	1.8E-04	3 M 1 F			2 M 1 F			1.9E-04		
52-100	3.4E-04	1 M 1 F			1 M 0 F			3.6E-04		
100-200	6.5E-04	1 M 0 F			1 M 0 F			7.0E-04		
200-400	1.3E-03	0 M 0 F								
400-800	2.5E-03	0 M 0 F								
800-4,000	1.0E-02	0 M 0 F								
> 4,000	1.7E-02	0 M 0 F								
Health Impact		**2.9E-02**			**2.2E-02**				**3.7E-03**	**2.6E-03**

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Table 4-11. Health Impact of the Simulated Incident for the Population Exposed to Acrylonitrile Following Damage of the Item "Unit Buffer Vessel", in Plant A

Concentration (ppm)	Cancer risk (adults)	Winter			Summer			Cancer risk (children)	Winter	Summer
		Workers	Adults	Elderly (> 65 years)	Workers	Adults	Elderly (> 65 years)		Children (< 18 years)	Children (< 18 years)
0.1-1	2.6E-05	60 M 14 F	205 M 222 F	60 M 65 F	63 M 16 F	145 M 157 F	42 M 46 F	2.8E-05	50 M 55 F	36 M 39 F
1-2.5	3.1E-05	37 M 9 F	8 M 9 F	2 M 3 F	41 M 10 F	3 M 3 F	1 M 1 F	3.3E-05	2 M 2 F	1 M 1 F
2.5-5	4.0E-05	27 M 6 F			19 M 5 F					
5-10	5.5E-05	14 M 3 F			10 M 2 F					
10-25	9.7E-05	8 M 2 F			6 M 1 F					
25-52	1.8E-04	3 M 1 F			2 M 0 F					
52-100	3.4E-04	1 M 0 F			1 M 0 F					
100-200	6.5E-04	1 M 0 F								
200-400	1.3E-03	0 M 0 F								
400-800	2.5E-03	0 M 0 F								
800-4,000	1.0E-02	0 M 0 F								
> 4,000	1.7E-02	0 M 0 F								
Health Impact		**2.3E-02**			**1.7E-02**				**3.1E-03**	**2.2E-03**

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Table 4-12. Health Impact of the Simulated Incident for the Population Exposed to Acrylonitrile Following Damage of the Item "Elastomer Production Reactor", in Plant A

Concentration (ppm)	Cancer risk (adults)	Winter			Summer			Cancer risk (children)	Winter	Summer
		Workers	Adults	Elderly (> 65 years)	Workers	Adults	Elderly (> 65 years)		Children (< 18 years)	Children (< 18 years)
0.1-1	2.6E-05	42 M 11 F	919 M 996 F	269 M 291 F	45 M 11 F	667 M 723 F	195 M 211 F	2.8E-05	226 M 245 F	164 M 178 F
1-2.5	3.1E-05	21 M 5 F	863 M 68 F	18 M 28 F	22 M 5 F	45 M 49 F	13 M 14 F	3.3E-05	16 M 20 F	11 M 12 F
2.5-5	4.0E-05	18 M 4 F	20 M 22 F	6 M 6 F	18 M 5 F	13 M 14 F	4 M 4 F	4.1E-05	5 M 5 F	3 M 4 F
5-10	5.5E-05	22 M 5 F	8 M 8 F	2 M 2 F	27 M 7 F	3 M 4 F	1 M 1 F	5.8E-05	2 M 2 F	1 M 1 F
10-25	9.7E-05	35 M 8 F	1 M 0 F		27 M 6 F					
25-52	1.8E-04	3 M 3 F			10 M 2 F					
52-100	3.4E-04	6 M 1 F			4 M 1 F					
100-200	6.5E-04	3 M 1 F			2 M 1 F					
200-400	1.3E-03	2 M 0 F			1 M 0 F					
400-800	2.5E-03	1 M 0 F			1 M 0 F					
800-4,000	1.0E-02	1 M 0 F								
> 4,000	1.7E-02	0 M 0 F								
Health Impact		**1.3E-01**			**7.0E-02**				**1.5E-02**	**1.1E-02**

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Table 4-13. Health Impact of the Simulated Incident for the Population Exposed to Acrylonitrile Following Damage of the Item "Stripping Column", in Plant A

Concentration (ppm)	Cancer risk (adults)	Winter			Summer			Cancer risk (children)	Winter	Summer
		Workers	Adults	Elderly (> 65 years)	Workers	Adults	Elderly (> 65 years)		Children (< 18 years)	Children (< 18 years)
0.1-1	2.6E-05	38 M 10 F	218 M 237 F	64 M 69 F	39 M 10 F	157 M 170 F	46 M 50 F	2.8E-05	54 M 58 F	39 M 42 F
1-2.5	3.1E-05	19 M 4 F	13 M 14 F	4 M 4 F	21 M 5 F	8 M 8 F	2 M 2 F	3.3E-05	3 M 3 F	2 M 2 F
2.5-5	4.0E-05	21 M 5 F	1 M 2 F	0 M 1 F	20 M 5 F			4.1E-05		
5-10	5.5E-05	14 M 4 F			10 M 3 F			5.8E-05		
10-25	9.7E-05	9 M 2 F			6 M 2 F			1.0E-04		
25-52	1.8E-04	3 M 1 F			2 M 1 F			1.9E-04		
52-100	3.4E-04	1 M 0 F			1 M 0 F			3.6E-04		
100-200	6.5E-04	1 M 0 F			1 M 0 F			7.0E-04		
200-400	1.3E-03	0 M 0 F								
400-800	2.5E-03	0 M 0 F								
800-4,000	1.0E-02	0 M 0 F								
> 4,000	1.7E-02	0 M 0 F								
Health Impact		**2.3E-02**			**1.8E-02**				**3.3E-03**	**2.4E-03**

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Table 4-14. Health Impact of the Simulated Incident for the Population Exposed to Acrylonitrile Following Simultaneous Damage of the Items "Acrylonitrile Storage Tank", "Unit Buffer Vessel", and "Stripping Column" in Plant A

Concentration (ppm)	Cancer risk (adults)	Winter			Summer			Cancer risk (children)	Winter	Summer
		Workers	Adults	Elderly (> 65 years)	Workers	Adults	Elderly (> 65 years)		Children (< 18 years)	Children (< 18 years)
0.1-1	2.6E-05	57 M 14 F	279 M 302 F	82 M 88 F	63 M 16 F	204 M 220 F	60 M 64 F	2.8E-05	69 M 74 F	50 M 54 F
1-2.5	3.1E-05	35 M 9 F	13 M 14 F	4 M 4 F	38 M 10 F	8 M 9 F	2 M 3 F	3.3E-05	3 M 3 F	2 M 2 F
2.5-5	4.0E-05	31 M 8 F	6 M 6 F	2 M 2 F	35 M 9 F	2 M 2 F	0 M 1 F	4.1E-05	1 M 1 F	
5-10	5.5E-05	34 M 8 F			28 M 7 F			5.8E-05		
10-25	9.7E-05	31 M 8 F			23 M 6 F			1.0E-04		
25-52	1.8E-04	9 M 2 F			6 M 2 F			1.9E-04		
52-100	3.4E-04	4 M 1 F			3 M 1 F			3.6E-04		
100-200	6.5E-04	2 M 1 F			2 M 0 F			7.0E-04		
200-400	1.3E-03	1 M 0 F			1 M 0 F					
400-800	2.5E-03	0 M 0 F								
800-4,000	1.0E-02	0 M 0 F								
> 4,000	1.7E-02	0 M 0 F								
Health Impact		**3.9E-02**			**3.1E-02**				**4.3E-03**	**3.0E-03**

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Table 4-15. Health Impact of the Simulated Incident for the Population Exposed to Acrylonitrile Following Simultaneous Damage of the Items "Acrylonitrile Storage Tank", "Unit Buffer Vessel", and "Elastomer Production Reactor" in Plant A

Concentration (ppm)	Cancer risk (adults)	Winter			Summer			Cancer risk (children)	Winter	Summer
		Workers	Adults	Elderly (> 65 years)	Workers	Adults	Elderly (> 65 years)		Children (< 18 years)	Children (< 18 years)
0.1-1	2.6E-05	56 M 14 F	920 M 997 F	269 M 291 F	60 M 15 F	668 M 723 F	195 M 211 F	2.8E-05	226 M 245 F	164 M 178 F
1-2.5	3.1E-05	27 M 7 F	63 M 69 F	18 M 20 F	28 M 7 F	45 M 49 F	13 M 14 F	3.3E-05	16 M 17 F	11 M 12 F
2.5-5	4.0E-05	19 M 5 F	20 M 22 F	6 M 6 F	21 M 5 F	13 M 14 F	4 M 4 F	4.1E-05	5 M 5 F	3 M 4 F
5-10	5.5E-05	24 M 6 F	8 M 8 F	2 M 2 F	36 M 9 F			5.8E-05	2 M 2 F	
10-25	9.7E-05	44 M 11 F	1 M		14 M 3 F			1.0E-04		
25-52	1.8E-04	18 M 5 F			6 M 2 F			1.9E-04		
52-100	3.4E-04	8 M 2 F			3 M 1 F			3.6E-04		
100-200	6.5E-04	5 M 1 F			2 M 0 F			7.0E-04		
200-400	1.3E-03	2 M 1 F			1 M 0 F					
400-800	2.5E-03	1 M 0 F								
800-4,000	1.0E-02	1 M 0 F								
> 4,000	1.7E-02	1 M 0 F								
Health Impact		**1.3E-01**			**6.5E-02**				**1.5E-02**	**1.1E-02**

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4.3 Arsenic

Table 4-16. Health Impact of the Simulated Incident for the Population Exposed to Arsenic Following Damage of the Items "Pregant solution tank" in Plant B

Concentration (ppm)	Cancer risk (adults)	Winter			Summer			Cancer risk (children)	Winter	Summer
		Workers	Adults	Elderly (> 65 years)	Workers	Adults	Elderly (> 65 years)		Children (< 18 years)	Children (< 18 years)
0.1-1	6.54E-04 5.45E-04	45 M 12 F	964 M 1012 F	289 M 302 F	54 M 18 F	698 M 754 F	207 M 225 F	6.69E-04 5.58E-04	234 M 259 F	174 M 188 F
1-2.5	7.08E-04 5.90E-04	23 M 6 F	76 M 74 F	23 M 31 F	26 M 8 F	49 M 55 F	18 M 17 F	7.25E-04 6.04E-04	18 M 23 F	13 M 15 F
2.5-5	7.96E-04 6.64E-04	20 M 5 F	24 M 23 F	7 M 8 F	19 M 7 F	18 M 17 F	4 M 5 F	8.08E-04 6.73E-04	6 M 6 F	4 M 5 F
5-10	9.63E-04 8.02E-04	24 M 6 F	9 M 8 F	3 M 3 F	32 M 8 F	5 M 6 F	2 M 2 F	9.86E-04 8.22E-04	3 M 3 F	2 M 1 F
10-25	1.41E-03 1.17E-03	38 M 9 F	1 M 0 F		27 M 8 F			1.46E-03 1.22E-03		
25-52	2.29E-03 1.91E-03	4 M 4 F			12 M 3 F			2.41E-03 2.01E-03		
52-100	3.96E-03 3.30E-03	7 M 1 F			5 M 2 F			4.19E-03 3.49E-03		
100-200	7.29E-03 6.07E-03	4 M 1 F			3 M 3 F					
200-400	1.39E-02 1.16E-02	2 M 1 F			2 M 1 F					
400-800	2.73E-02 2.27E-02	1 M 0 F			1 M 0 F					
800-4,000	1.07E-01 8.93E-02	1 M 0 F								
> 4,000	1.78E-01 1.49E-01	0 M 0 F								
Health Impact		**2.2E+00**			**1.6E+00**				**3.4E-01**	**2.5E-01**

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Table 4-17. Health Impact of the Simulated Incident for the Population Exposed to Arsenic Following Damage of the Items "Leach thickener" in Plant B

Concentration (ppm)	Cancer risk (adults)	Winter			Summer			Cancer risk (children)	Winter	Summer
		Workers	Adults	Elderly (> 65 years)	Workers	Adults	Elderly (> 65 years)		Children (< 18 years)	Children (< 18 years)
0.1-1	6.54E-04 5.45E-04	35 M 9 F	412 M 267 F	124 M 143 F	45 M 12 F	299 M 332 F	92 M 94 F	6.69E-04 5.58E-04	109 M 116 F	79 M 85 F
1-2.5	7.08E-04 5.90E-04	41 M 10 F	29 M 31 F	8 M 9 F	64 M 16 F	17 M 18 F	5 M 3 F	7.25E-04 6.04E-04	7 M 9 F	5 M 4 F
2.5-5	7.96E-04 6.64E-04	59 M 15 F	8 M 7 F	2 M 2 F	59 M 15 F	2 M 1 F	1 M 1 F	8.08E-04 6.73E-04	2 M 2 F	1 M 1 F
5-10	9.63E-04 8.02E-04	43 M 11 F	1 M 1 F		43 M 11 F			9.86E-04 8.22E-04		
10-25	1.41E-03 1.17E-03	56 M 14 F			29 M 7 F			1.46E-03 1.22E-03		
25-52	2.29E-03 1.91E-03	39 M 10 F			9 M 2 F			2.41E-03 2.01E-03		
52-100	3.96E-03 3.30E-03	13 M 3 F			4 M 1 F			4.19E-03 3.49E-03		
100-200	7.29E-03 6.07E-03	6 M 1 F			3 M 0 F					
200-400	1.39E-02 1.16E-02	4 M 1 F			1 M 0 F					
400-800	2.73E-02 2.27E-02	1 M 0 F								
800-4,000	1.07E-01 8.93E-02	0 M 0 F								
> 4,000	1.78E-01 1.49E-01	0 M 0 F								
Health Impact		**1.2E+00**			**8.5E-01**				**1.5E-01**	**1.1E-01**

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Table 4-18. Health Impact of the Simulated Incident for the Population Exposed to Arsenic Following Damage of the Items "High share pre-oxidation", "Cyanide leach circuit", Cyanide destruction" and "Strip circuit" in Plant B.

Concentration (ppm)	Cancer risk (adults)	Winter			Summer			Cancer risk (children)	Winter	Summer
		Workers	Adults	Elderly (> 65 years)	Workers	Adults	Elderly (> 65 years)		Children (< 18 years)	Children (< 18 years)
0.1-1	6.54E-04 5.45E-04	39 M 11 F	218 M 237 F	64 M 69 F	44 M 13 F	168 M 189 F	53 M 55 F	6.69E-04 5.58E-04	58 M 62 F	43 M 47 F
1-2.5	7.08E-04 5.90E-04	19 M 4 F	13 M 14 F	4 M 4 F	21 M 5 F	8 M 8 F	3 M 3 F	7.25E-04 6.04E-04	3 M 3 F	3 M 2 F
2.5-5	7.96E-04 6.64E-04	22 M 5 F	1 M 2 F	0 M 1 F	22 M 5 F			8.08E-04 6.73E-04		
5-10	9.63E-04 8.02E-04	16 M 7 F			10 M 3 F			9.86E-04 8.22E-04		
10-25	1.41E-03 1.17E-03	10 M 2 F			6 M 2 F			1.46E-03 1.22E-03		
25-52	2.29E-03 1.91E-03	3 M 1 F			2 M 1 F			2.41E-03 2.01E-03		
52-100	3.96E-03 3.30E-03	1 M 0 F			1 M 0 F			4.19E-03 3.49E-03		
100-200	7.29E-03 6.07E-03	1 M 0 F			1 M 0 F					
200-400	1.39E-02 1.16E-02	0 M 0 F								
400-800	2.73E-02 2.27E-02	0 M 0 F								
800-4,000	1.07E-01 8.93E-02	0 M 0 F								
> 4,000	1.78E-01 1.49E-01	0 M 0 F								
Health Impact		**5.0E-01**			**4.1E-01**				**7.7E-02**	**5.8E-02**

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