

## Sample Level of Concern Card Scenarios

The screenshot shows a web application interface for 'Level of Concern'. A modal window is open for the question '1: What is your Level of Concern for men?'. The form contains the following sections:

- Hazard:** Presumed
- Human evidence:** *Inadequate evidence*. Below this, it states 'No studies available.'
- Animal evidence:** *High evidence*
- Mechanistic/other evidence:** (This field is currently empty)
- Exposure:** (This section is highlighted in blue)
- Exposure description:** (This field is currently empty)
- LoC category:** A dropdown menu is set to 'Uncategorized'. Below it, instructions state: 'Select which category to place this card. Concern increases as category number increases.'

Buttons for 'Save' and 'Close' are visible at the bottom of the modal. The background shows a sidebar with other questions and a 'Submit Board' button.

## 1. What is your level of concern for neonatal intensive care unit (NICU) infants?

**Hazard:** Presumed**Human evidence:** *Inadequate evidence*

No studies available.

**Animal evidence:** *High evidence*

Exposure of pregnant rats to dosed feed during gestation and postnatal development resulted in exposure levels of 14 to 23 mg/kg bw/day to mothers and was associated with adverse effects on development of the male reproductive tract including small or absent reproductive organs, skeletal and cardiovascular malformations, neural tube defects, developmental delays, and intrauterine death of offspring. The frequency of the adverse effects ranged from 5-20% and there was evidence for a monotonic dose-response gradient.

**Mechanistic/other evidence**

No impact on hazard identification classification.

**Exposure****Exposure description**

Exposure in women of childbearing age is estimated to be 0.6 mg/kg bw/day based on back-calculation from urinary metabolites measured in NHANES.

Margin of Exposure (MOE) of 23 to 38 based on comparing administered dose in animal study (14 to 23 mg/kg bw/day) to estimated daily intake in women (0.6 mg/kg bw/day).

**Other information**

High productive volume chemical.

## 2. What is your Level of Concern for women of childbearing age?

<b>Hazard: Presumed</b>
<b>Human evidence: <i>Inadequate evidence</i></b> No studies available.
<b>Animal evidence: <i>High evidence</i></b> Exposure of pregnant rats to dosed feed during gestation and postnatal development resulted in exposure levels of 14 to 23 mg/kg bw/day to mothers and was associated with adverse effects on development of the male reproductive tract including small or absent reproductive organs, skeletal and cardiovascular malformations, neural tube defects, developmental delays, and intrauterine death of offspring. The frequency of the adverse effects ranged from 5-20% and there was evidence for a monotonic dose-response gradient.
<b>Mechanistic/other evidence</b> No impact on hazard identification classification.
<b>Exposure</b>
<b>Exposure description</b> Exposure in women of childbearing age is estimated to be 0.6 mg/kg bw/day based on back-calculation from urinary metabolites measured in NHANES.  Margin of Exposure (MOE) of 23 to 38 based on comparing administered dose in animal study (14 to 23 mg/kg bw/day) to estimated daily intake in women (0.6 mg/kg bw/day).
<b>Other information</b> High productive volume chemical.

## 3. What is your Level of Concern for men?

<b>Hazard: Presumed</b>
<b>Human evidence: <i>Inadequate evidence</i></b> No studies available.
<b>Animal evidence: <i>High evidence</i></b> Exposure of pregnant rats to dosed feed during gestation and postnatal development resulted in exposure levels of 14 to 23 mg/kg bw/day to mothers and was associated with adverse effects on development of the male reproductive tract including small or absent reproductive organs, skeletal and cardiovascular malformations, neural tube defects, developmental delays, and intrauterine death of offspring. The frequency of the adverse effects ranged from 5-20% and there was evidence for a monotonic dose-response gradient.
<b>Mechanistic/other evidence</b> No impact on hazard identification classification.
<b>Exposure</b>
<b>Exposure description</b> Exposure in men estimated to be 0.6 mg/kg bw/day based on back-calculation from urinary metabolites measured in NHANES.  Margin of Exposure (MOE) of 23 to 38 based on comparing administered dose in animal study (14 to 23 mg/kg bw/day) to estimated daily intake in men (0.6 mg/kg bw/day).
<b>Other information</b> High productive volume chemical.

## 4. What is your Level of Concern for exposed workers?

<b>Hazard: Suspected</b>
<b>Human evidence: <i>Inadequate evidence</i></b> No studies available.
<b>Animal evidence: <i>Moderate evidence</i></b> Oral exposure of pregnant rats to ~5-8 mg/kg bw/day resulted in lower body weights in offspring of ~25%. Dam weights were not affected. The level of evidence was downgraded from high to moderate because there was unexplained inconsistency in body weight findings across four studies, i.e., two did not detect a difference.
<b>Mechanistic/other evidence</b> No impact on hazard identification classification.
<b>Exposure</b>
<b>Exposure description</b> Inhalation exposure in exposed female workers of childbearing age is estimated as high as 0.043 mg/kg bw/day based on data from a small number of work sites that was collected 15 years ago.  Margin of Exposure (MOE) of 116 to 186 based on administered dose level resulting in lower body weights in offspring in animal developmental toxicity study (5-8 mg/kg bw/day) compared to estimated occupational exposure levels in women (0.043 mg/kg bw/day).
<b>Other information</b> No other information.

## 5. What is your Level of Concern for the general population?

<b>Hazard: Not classifiable</b>
<b>Human evidence: <i>Inadequate evidence</i></b> No studies available.
<b>Animal evidence: <i>Low evidence</i></b> Oral exposure to pregnant dams at $\geq 500$ mg/kg bw/day (mice) or at $\geq 1000$ mg/kg bw/day (rats) resulted in fetal deaths (10%), skeletal and external malformations (15%), and reduced body weights among offspring (up to 10%). Maternal toxicity observed at the same dose levels. The level of evidence was downgraded from high to low based on (1) concern for risk of bias (internal validity), and (2) unexplained inconsistency because two other studies in mice of similar design reported effects at similar dose levels.
<b>Mechanistic/other evidence</b> No impact on hazard identification classification.
<b>Exposure</b>
<b>Exposure description</b> Oral exposure in adults estimated to range from 0.125 to 1.25 mg/kg bw/day based on typical therapeutic dosing regimens.  Margin of Exposure (MOE) range of 400 to 4,000 based on administered dose level resulting in developmental toxicity in animals ( $\geq 500$ mg/kg bw/day) compared to doses used clinically (0.125 to 1.25).
<b>Other information</b> Industrial chemical.

## 6. What is your Level of Concern for women of childbearing age?

<b>Hazard: Presumed</b>
<b>Human evidence: <i>Inadequate evidence</i></b> No studies available that address neurological outcomes.
<b>Animal evidence: <i>Moderate evidence</i></b> Oral exposure $\geq 500$ mg/kg bw/day in rats and mice treated during gestation and/or during early post-natal life in several studies resulted in impaired performance in learning and memory tests. The level of evidence was downgraded from high to moderate based on concern for risk of bias (internal validity) in most of the studies.
<b>Mechanistic/other evidence</b> Raises the hazard identification classification from "suspected" to "presumed." Mechanistic data from in vivo studies shows the chemical can decrease thyroid hormone levels and in vitro studies show impaired neuronal development at relatively low concentrations ( $<10$ $\mu$ M).
<b>Exposure</b>
<b>Exposure description</b> Oral exposure in adults estimated to range from 0.125 to 1.25 mg/kg bw/day based on typical therapeutic dosing regimens.  Margin of Exposure (MOE) range of 400 to 4,000 based on administered dose level resulting in developmental neurotoxicity in animals ( $\geq 500$ mg/kg bw/day) compared to doses used clinically (0.125 to 1.25 mg/kg bw/day).
<b>Other information</b> Pharmaceutical.

## 7. What is your Level of Concern for females of childbearing age?

<b>Hazard: Presumed</b>
<b>Human evidence: <i>Inadequate evidence</i></b> No studies available.
<b>Animal evidence: <i>High evidence</i></b> Dietary treatment of 250 to 1000 mg/kg bw/day to female mice resulted in effects on reproduction and carcinogenesis. Body weights were slightly lower in the highest treated mice; decreased relative weight of the thymus and liver and lower uterine size were found at the two highest doses (750 and 1000 mg/kg bw/day). Effects on reproduction included longer estrous cycles at 500 mg/kg bw/day; at 750 mg/kg bw/day, longer estrous cycle and lower fertility; and at 1000 mg/kg bw/day, longer estrous cycle, lower fertility, and smaller litter sizes. In a separate group of animals, similar effects on body weight and organ weights were found along with dose-related increases (500 to 1000 mg/kg bw/day) in ovarian and mammary tumors.
<b>Mechanistic/other evidence</b> No impact on hazard identification classification.
<b>Exposure</b>
<b>Exposure description</b> Dietary exposure of general population is estimated at $<0.002$ mg/kg bw/day.  Margin of Exposure (MOE) range of 250,000 is based on estimated dietary intake in humans (0.002 mg/kg bw/day) and the lowest dose levels in animal studies (500 mg/kg bw/day) that caused reproductive toxicity and had carcinogenic activity.
<b>Other information</b> No other information.

## 8. What is your Level of Concern for exposed workers?

<b>Hazard: Not classifiable</b>
<p><b>Human evidence: Low evidence</b></p> <p>A case-control analysis in an occupational setting showed a significant association with diabetes. The level of evidence was downgraded from high to low based on (1) lack of controlled exposure, and (2) the study design did not allow a determination of whether exposure preceded the health outcome.</p>
<p><b>Animal evidence: Low evidence</b></p> <p>Oral exposure to rat dams at <math>\geq 200</math> mg/kg bw/day resulted in pancreatic toxicity and impaired glucose tolerance. The level of evidence was downgraded from high to low based on (1) concern for risk of bias (internal validity), and (2) concern for publication bias, i.e., all three studies came from the same research group and used a small number of animals.</p>
<p><b>Mechanistic/other evidence</b></p> <p>No impact on hazard identification classification.</p>
<b>Exposure</b>
<p><b>Exposure description</b></p> <p>Inhalation exposure of workers ranges from 1.4 to 90 mg/kg bw/day.</p> <p>Margin of Exposure (MOE) range of <math>\sim 2</math> to 145 is based on estimated human occupational exposure administered dose level resulting in effects in animals (<math>\geq 200</math> mg/kg bw/day).</p>
<p><b>Other information</b></p> <p>No other information.</p>

## 9. What is your Level of Concern for exposed workers?

<b>Hazard: Presumed</b>
<p><b>Human evidence: Low evidence</b></p> <p>An occupational case-control study reported an increase in liver transaminases [aspartate aminotransferase (AST), alanine aminotransferase (ALT)] used as biomarkers for liver injury and increases in serum cholesterol and triglycerides in exposed workers. Considered low quality evidence because of (1) lack of controlled exposure, and (2) concern for risk of bias (internal validity) related to quality of the exposure assessment.</p>
<p><b>Animal evidence: High evidence</b></p> <p>Dietary treatment to male and female rats of <math>\geq 200</math> mg/kg/day caused increased blood pressure and treatment at higher doses of <math>\geq 500</math> mg/kg bw/day caused histopathological findings in the heart in males. In a rabbit teratology study, drinking water exposure to <math>\geq 1000</math> mg/kg/day resulted in skeletal abnormalities, cleft palates, exencephaly (the brain is located outside of the skull), and skeletal malformations.</p>
<p><b>Mechanistic/other evidence</b></p> <p>No impact on hazard identification classification.</p>
<b>Exposure</b>
<p><b>Exposure description</b></p> <p>Human exposure levels not quantified, based on job occupation and assumed relative level of exposure.</p> <p>Margin of Exposure (MOE) is unknown.</p>
<p><b>Other information</b></p> <p>Occupational exposure and chemical can be found in consumer products.</p>

## 10. What is your Level of Concern for the general population?

<b>Hazard: Presumed</b>
<p><b>Human evidence: <i>Low evidence</i></b></p> <p>An occupational case-control study reported an increase in liver transaminases [aspartate aminotransferase (AST), alanine aminotransferase (ALT)] used as biomarkers for liver injury and increases in serum cholesterol and triglycerides in exposed workers. Considered low quality evidence because of (1) lack of controlled exposure, and (2) concern for risk of bias (internal validity) related to quality of the exposure assessment.</p>
<p><b>Animal evidence: <i>High evidence</i></b></p> <p>Dietary treatment to male and female rats of <math>\geq 200</math> mg/kg/day caused increased blood pressure and treatment at higher doses of <math>\geq 500</math> mg/kg/day caused histopathological findings in the heart in males. In a rabbit teratology study, drinking water exposure to <math>\geq 1000</math> mg/kg/day resulted in skeletal abnormalities, cleft palates, exencephaly (the brain is located outside of the skull), and skeletal malformations.</p>
<p><b>Mechanistic/other evidence</b></p> <p>No impact on hazard identification classification.</p>
<b>Exposure</b>
<p><b>Exposure description</b></p> <p>Human exposure levels not quantified, based on job occupation and assumed relative level of exposure.</p> <p>Margin of Exposure (MOE) is unknown.</p>
<p><b>Other information</b></p> <p>Occupational exposure and chemical can be found in consumer products.</p>

## 11. What is your Level of Concern for exposed female workers?

<b>Hazard: Suspected</b>
<p><b>Human evidence: <i>Inadequate evidence</i></b></p> <p>A case series report of 3 women occupationally exposed to 60-260 ppm (time weighted average) reported altered menstrual cycles in 2 women. The level of evidence was downgraded from high to very low based on (1) lack of controlled exposure, (2) the study design did not allow a determination of whether exposure preceded the health outcome, and (3) lack of a comparison group.</p>
<p><b>Animal evidence: <i>Moderate evidence</i></b></p> <p>Inhalation exposure of rats to <math>\geq 750</math> ppm decreased prostate weight, sperm motility, and percent normal sperm in males. The level of evidence was downgraded from high to moderate because there was concern for risk of bias (internal validity).</p>
<b>Exposure</b>
<p><b>Mechanistic/other evidence</b></p> <p>No impact on hazard identification classification.</p>
<p><b>Exposure description</b></p> <p>Inhalation exposure to workers ranges from 60-260 ppm based on air measurements in workplace.</p> <p>Margin of Exposure (MOE) of <math>\sim 3</math> to 13 is based on comparing inhalation exposures that resulted in effects on the male reproductive system in rats (<math>\geq 750</math> ppm) to the range of exposures reported in occupational settings (60-260 ppm).</p>
<p><b>Other information</b></p> <p>No other information.</p>

## 12. What is your Level of Concern for exposed male workers?

<b>Hazard: Suspected</b>
<p><b>Human evidence: <i>Inadequate evidence</i></b></p> <p>A case series report of 3 women occupationally exposed to 60-260 ppm (time weighted average) reported altered menstrual cycles in 2 women. The level of evidence was downgraded from high to very low based on (1) lack of controlled exposure, (2) the study design did not allow a determination of whether exposure preceded the health outcome, and (3) lack of a comparison group.</p>
<p><b>Animal evidence: <i>Moderate evidence</i></b></p> <p>Inhalation exposure of rats to <math>\geq 750</math> ppm decreased prostate weight, sperm motility, and percent normal sperm in males. The level of evidence was downgraded from high to moderate because there was concern for risk of bias (internal validity).</p>
<p><b>Mechanistic/other evidence</b></p> <p>No impact on hazard identification classification.</p>
<b>Exposure</b>
<p><b>Exposure description</b></p> <p>Inhalation exposure to workers ranges from 60-260 ppm based on air measurements in workplace.</p> <p>Margin of Exposure (MOE) of <math>\sim 3</math> to 13 is based on comparing inhalation exposures that resulted in effects on male reproductive system in rats (<math>\geq 750</math> ppm) to the range of exposures reported in occupational settings (60-260 ppm).</p>
<p><b>Other information</b></p> <p>No other information.</p>

## 13. What is your Level of Concern for exposed female workers?

<b>Hazard: Not classifiable</b>
<p><b>Human evidence: <i>Inadequate evidence</i></b></p> <p>A case series report of 3 women occupationally exposed to 60-260 ppm (time weighted average) reported altered menstrual cycles in 2 women. The level of evidence was downgraded from high to very low based on (1) lack of controlled exposure, (2) the study design did not allow a determination of whether exposure preceded the health outcome, and (3) lack of comparison group.</p>
<p><b>Animal evidence: <i>Low evidence</i></b></p> <p>Inhalation exposure of rats to <math>\geq 250</math> ppm for 10 weeks decreased litter size, increased ovarian follicular cysts, and increased estrous cycle length in females. The level of evidence was downgraded from high to low based on (1) concern for risk of bias (internal validity), and (2) unexplained inconsistency with two other studies in rats of similar design that reported effects at similar dose levels.</p>
<p><b>Mechanistic/other evidence</b></p> <p>No impact on hazard identification classification.</p>
<b>Exposure</b>
<p><b>Exposure description</b></p> <p>Inhalation exposure to workers ranges from 60-260 ppm based on air measurements in workplace.</p> <p>Margin of Exposure (MOE) of less than 1 to <math>\sim 4</math> is based on comparing inhalation exposures that resulted in effects on female reproductive system in rats (<math>\geq 250</math> ppm) to the range of exposures reported in occupation settings (60-260 ppm).</p>
<p><b>Other information</b></p> <p>No other information.</p>

## 14. What is your Level of Concern for women of childbearing age outside of the occupational setting?

<b>Hazard: Known</b>
<p><b>Human evidence: Moderate evidence</b></p> <p>Two case-control studies in female workers showed associations between exposure and birth defects in male offspring (hypospadias). The level of evidence was downgraded from high to moderate because the studies did not have controlled exposure (i.e., they were observational in design rather than randomized trial).</p>
<p><b>Animal evidence: Moderate evidence</b></p> <p>Oral gavage administration of female rats to &gt;500 mg/kg bw/day during gestation resulted in reduced litter size and body weight of offspring, skeletal malformations, and abnormalities of the reproductive organs in male and female offspring. Male offspring had reductions in testicular testosterone levels. The level of evidence was downgraded from high to moderate because there was concern for risk of bias (internal validity).</p>
<p><b>Mechanistic/other evidence</b></p> <p>Raises the hazard identification classification from "presumed" to "known." The compound is accepted as having anti-androgenic activity, which would be expected to affect male reproductive tract development.</p>
<b>Exposure</b>
<p><b>Exposure description</b></p> <p>Exposure to the general population is 0.002-0.010 mg/kg bw/day based on urinary biomonitoring data. At the high end, based on worst-case assumption models, exposures up to ~0.1 mg/kg bw/day are possible with regular use of certain consumer products.</p> <p>Margin of Exposure (MOE) of 5000 is based on the lowest exposure level resulting in developmental toxicity (500 mg/kg bw/day) and the highest estimated exposure level in non-workers (0.1 mg/kg bw/day).</p>
<p><b>Other information</b></p> <p>Steps were taken in occupational settings to reduce exposure (worker protection clothing and finding alternatives).</p>

## 15. What is your Level of Concern for women of childbearing age?

<b>Hazard: Presumed</b>
<p><b>Human evidence: Moderate evidence</b></p> <p>A meta-analysis of nine observational human studies estimated that a 1 ng/mL increase in serum or plasma levels was associated with a -18.9 g (95% CI: -29.8, -7.9) difference in birth weight. The level of evidence was downgraded from high to moderate because the studies did not have controlled exposure (i.e., they were observational in design rather than randomized trial).</p>
<p><b>Animal evidence: Moderate evidence</b></p> <p>A meta-analysis of eight gavage studies in mice resulted in the conclusion that exposure of pregnant mice to increasing concentrations was associated with a decrease in mean pup birth weight of -0.023g (95% CI: -0.029, -0.016) per 1-unit increase in dose (mg/kg bw/day). The level of evidence was downgraded from high to moderate because there was concern for risk of bias (internal validity).</p>
<p><b>Mechanistic/other evidence</b></p> <p>No impact on hazard identification classification.</p>
<b>Exposure</b>
<p><b>Exposure description</b></p> <p>The nine human studies included in the meta-analysis were general population studies.</p> <p>No Margin of Exposure (MOE) based on human studies because an association is being reported at current blood levels in the general population.</p>
<p><b>Other information</b></p> <p>No other information.</p>

## 16. What is your Level of Concern for exposed female workers?

<b>Hazard: Presumed</b>
<b>Human evidence: <i>Inadequate evidence</i></b> No studies available.
<b>Animal evidence: <i>High evidence</i></b> Inhalation exposure of male and female rats, 6 hours/day, 7 days/week, was carried out for at least 70 days prior to mating. Exposure levels ranged from 100 ppm to 750 ppm. No adverse effects were observed at 100 ppm. Statistically significant effects included lower prostate weights at 250 ppm; longer estrous cycles, lower fertility, smaller litter sizes, lower sperm motility, and lower prostate weights at 500 ppm; and at 750 ppm, longer estrous cycles, lower sperm motility, lower prostate weights, lower ovary weights, fewer corpora lutea, and no conceptions. In a second, smaller study (8 or 9 males/group) of male reproductive effects, rats were exposed to 200, 400, or 800 ppm, 8 hours/day for 12 weeks. Seminal vesicle weights were lower at 200 ppm. At 400 and 800 ppm, seminal vesicle weights, sperm counts, and motile sperm were all significantly lower.
<b>Mechanistic/other evidence</b> No impact on hazard identification classification.
<b>Exposure</b>
<b>Exposure description</b> Exposure levels in worker breathing zones in one occupational setting are reported to be 0.05 to 0.65 ppm.  Margin of Exposure (MOE) of ~300 based on lowest exposure level that resulted in reproductive effects in male rodents (200 ppm) compared to the high end of the exposure range reported in an occupational setting (0.65 ppm).
<b>Other information</b> No other information.

## 17. What is your Level of Concern for exposed workers?

<b>Hazard: Not classifiable</b>
<b>Human evidence: <i>Inadequate evidence</i></b> No studies available.
<b>Animal evidence: <i>Inadequate evidence</i></b> No studies available.
<b>Mechanistic/other evidence</b> No impact on hazard identification classification; high throughput screening data show activity in several nuclear receptor activation assays at concentrations from 1 to 10 $\mu$ M.
<b>Exposure</b>
<b>Exposure description</b> Exposure levels in worker breathing zones in one occupational setting are reported to be 0.05 to 0.65 ppm.  Margin of Exposure (MOE) is unknown.
<b>Other information</b> Occupational exposure is episodic, i.e., peak and average levels differ across a 100-fold range.

## 18. What is your Level of Concern for pregnant women living at a Superfund site?

<b>Hazard: Presumed</b>
<p><b>Human evidence: <i>Moderate evidence</i></b>  Several prospective studies at Superfund sites report significant associations with reduced IQ in children. The level of evidence was downgraded from high to moderate because the studies did not have controlled exposure (i.e., they were observational in design rather than a randomized trial).</p>
<p><b>Animal evidence: <i>Low evidence</i></b>  Developmental neurotoxicity was reported in a collection of rat and mouse studies at oral doses ranging from 20 to 80 mg/kg bw/day (either to the dam or directly to offspring after weaning). The studies reported effects on different aspects of neurotoxicity, including learning and memory and reflex development. The level of evidence was downgraded from high to low based on concern for (1) risk of bias (internal validity), and (2) publication bias.</p>
<p><b>Mechanistic/other evidence</b>  Raises the hazard identification classification from "suspected" to "presumed." The chemical has been shown to reduce thyroid hormone levels in rodents and inhibit neuronal growth in culture systems at concentrations less than 10 µM.</p>
<b>Exposure</b>
<p><b>Exposure description</b>  Exposure levels from all sources of exposure at Superfund sites estimated at 15 to 35 mg/kg bw/day.</p> <p>Margin of Exposure (MOE) of ~1 to 5 based on lowest daily oral dose that resulted in developmental effects in rodents (20 to 80 mg/kg bw/day) compared to the daily oral exposure in humans (15 to 35 mg/kg bw/day).</p>
<p><b>Other information</b>  No other information.</p>

## 19. What is your Level of Concern for female workers?

<b>Hazard: Presumed</b>
<p><b>Human evidence: <i>Moderate evidence</i></b>  Eight studies reported relative significant risk estimates for histologically confirmed breast cancer in female workers exposed to the chemical. Two were prospective cohort studies, one was a nationwide census-based cohort study, three were nested case-control studies, and two were retrospective case-control studies. The level of evidence was downgraded from high to moderate because the studies did not have controlled exposure (i.e., they were observational in design rather than a randomized trial).</p>
<p><b>Animal evidence: <i>Inadequate evidence</i></b>  No studies available.</p>
<p><b>Mechanistic/other evidence</b>  Raises the hazard identification classification from "suspected" to "presumed." The chemical decreases secretion of melatonin; greater secretion of melatonin is associated with a lower risk of breast cancer.</p>
<b>Exposure</b>
<p><b>Exposure description</b>  Exposure is assumed to be mostly occupational, but has not been quantified.</p> <p>No Margin of Exposure (MOE) for workers because an association is being reported in occupational settings.</p>
<p><b>Other information</b>  No other information.</p>

## 20. What is your Level of Concern for the general population?

<b>Hazard: Suspected</b>
<p><b>Human evidence: <i>Moderate evidence</i></b></p> <p>Five studies reported relative significant risk estimates for cardiovascular effects in men exposed to the chemical. Two were prospective cohort studies, two were nested case-control studies, and one was a retrospective case-control studies. The level of evidence was downgraded from high to moderate because the studies did not have controlled exposure (i.e., they were observational in design rather than a randomized trial).</p>
<p><b>Animal evidence: <i>Inadequate evidence</i></b></p> <p>No studies available.</p>
<p><b>Mechanistic/other evidence</b></p> <p>No impact on hazard identification classification.</p>
<b>Exposure</b>
<p><b>Exposure description</b></p> <p>Exposure of the general population is estimated to be less than 0.003 mg/kg bw/day; exposure in workers is estimated at 3 to 30 mg/kg/day.</p> <p>Margin of Exposure (MOE) of approximately 1,000 to 10,000 based on levels in occupational settings compared to general population.</p>
<p><b>Other information</b></p> <p>No other information.</p>

## 21. What is your Level of Concern for men who take this drug?

<b>Hazard: Suspected</b>
<p><b>Human evidence: <i>Inadequate evidence</i></b></p> <p>There is one case report of azoospermia (absence of motile sperm in semen) in a man being treated with this drug. The level of evidence was initially considered low because there was no comparison group or analysis of sperm count in the man before or after treatment was stopped, and further downgraded to very low because of low sample size (n=1).</p>
<p><b>Animal evidence: <i>Moderate evidence</i></b></p> <p>Reproductive toxicity has been evaluated in two rat studies. In one study, mature males were exposed to 75 mg/kg bw/day in drinking water for 70 days (a single dose level study). At the end of treatment, weight of the testes was 55% lower than in control males and numerous histological abnormalities were observed in the seminiferous tubules. In a second rat study, mature males were exposed to 50 mg/kg bw/day in drinking water for 3 months. At the end of exposure, testis and caput epididymis weights and serum luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels were significantly lower than in the controls. Data on adverse effects on male fertility in laboratory animals were not available. The level of evidence was downgraded from high to low based on concern for (1) indirectness (i.e., not having measurement of fertility).</p>
<p><b>Mechanistic/other evidence</b></p> <p>Raises the hazard identification categorization from "suspected" to "presumed." Known to deplete deoxyribonucleotide pools thereby inhibiting DNA synthesis. This provides a feasible mechanism for lowered sperm counts and increases confidence in the hazard identification conclusion.</p>
<b>Exposure</b>
<p><b>Exposure description</b></p> <p>People who take this drug receive from 20 to 40 mg/kg bw/day. It is taken orally.</p> <p>Margin of Exposure (MOE) is approximately 1.3 to 2 based on comparison of peak plasma concentrations in rats treated with 50 mg/kg bw/day and humans taking 25 to 40 mg/kg bw/day orally.</p>
<p><b>Other information</b></p> <p>No other information.</p>

## 22. What is your Level of Concern for pregnant women in the general population?

<b>Hazard: Suspected</b>
<b>Human evidence: <i>Inadequate evidence</i></b> No studies available.
<b>Animal evidence: <i>Moderate evidence</i></b> There are four developmental toxicity studies in rats, all using Sprague-Dawley rats treated via drinking water from pre-mating through weaning. Each study had three treatment groups and tested a similar range of doses (0, 20 to 120 mg/kg bw/day). Neurotoxicity was observed in all treatment groups in two of the studies; no effects were reported in the other two studies. The level of evidence was downgraded from high to low based on concern for (1) inconsistency of results that could not be explained.
<b>Mechanistic/other evidence</b> No impact on hazard identification classification.
<b>Exposure</b>
<b>Exposure description</b> Exposure of the general population is estimated to range from 0.0009 to 0.0035 mg/kg bw/day.  Margin of Exposure (MOE) of ~5,700 to 34,000 based on estimated human exposure in the general population (0.0009 to 0.0035 mg/kg bw/day) and levels inducing developmental neurotoxicity in rodents (at 20 to 120 mg/kg bw/day).
<b>Other information</b> No other information.

## 23. What is your Level of Concern for exposed male workers?

<b>Hazard: Known</b>
<b>Human evidence: <i>High evidence</i></b> The chemical was previously used as a pharmaceutical that was prescribed to pregnant women to prevent miscarriage. Shortly after its introduction for this use, hundreds of cases of a rare congenital deformity were reported in babies whose mothers took the drug. The deformity was similar to one identified in animal studies conducted after the human reports began to appear. Although these human studies were not controlled trials, the level of evidence was considered high because of the rarity of the deformity in babies whose mothers did not take the drug and the magnitude of the association in women who did.
<b>Animal evidence: <i>High evidence</i></b> Oral gavage of pregnant rats with 200 mg/kg bw/day on gestation days 7 to 20 or 300 mg/kg bw/day on gestation days 6 to 15 resulted in a higher rate of a rare limb malformation, lower body weights, and a lower number of live pups. Similar effects were reported for pregnant rats following dietary treatment with 100 mg/kg bw/day on gestations days 9 to 12 and in pregnant mice treated with 200 mg/kg bw/day by oral gavage on gestation days 6 to 17. In both species, the most commonly reported malformations were limb deformities, cleft palate, vertebral abnormalities, and deformities of the toes.
<b>Mechanistic/other evidence</b> No impact on hazard identification classification.
<b>Exposure</b>
<b>Exposure description</b> Occupational exposures range from 0.01 to 0.1 mg/kg bw/day.  Margin of Exposure (MOE) of 2,000 to 20,000 based on estimated occupational exposure levels (0.01 to 0.1 mg/kg bw/day) and dose levels in animal studies that caused developmental toxicity ( $\geq 200$ mg/kg/day).
<b>Other information</b> No other information.

## 24. What is your Level of Concern for general population?

<b>Hazard: Not classifiable</b>
<b>Human evidence: <i>Inadequate evidence</i></b> No studies available.
<b>Animal evidence: <i>Inadequate evidence</i></b> A single study reported no effects in mice dosed with 50, 75, or 150 mg/kg bw/day. The level of evidence was downgraded from high to low because the study had numerous internal validity issues (i.e., no randomization to groups, no blinding at outcome assessment, and no reporting of purity or source of compound). In addition, the study was statistically underpowered.
<b>Mechanistic/other evidence</b> No impact on hazard identification classification.
<b>Exposure</b>
<b>Exposure description</b> No data available on human exposure levels.  Margin of Exposure (MOE) is unknown.
<b>Other information</b> No other information.

## 25. What is your Level of Concern for infants and children in the general population?

<b>Hazard: Presumed</b>
<b>Human evidence: <i>Moderate evidence</i></b> Several prospective, cohort studies in children have shown an increased risk for respiratory disease and otitis media, and reduced efficacy of vaccination. The level of evidence was downgraded from high to moderate because the studies did not have controlled exposure (i.e., they were observational in design rather than randomized control trials).
<b>Animal evidence: <i>High evidence</i></b> Numerous studies in rodents and primates indicate that several chemicals in this class of compounds suppress immune function. The effect of suppressed immune function occurred following adult and/or developmental exposures at dose levels ranging from 10 to 100 mg/kg bw/day.
<b>Mechanistic/other evidence</b> No impact on hazard identification classification.
<b>Exposure</b>
<b>Exposure description</b> There are infectious disease (vaccine) studies in an isolated population with relatively high exposure via the diet (~1 mg/kg bw/day). Other findings are reported in the general population with estimated exposure of 0.01 mg/kg bw/day.  Margin of Exposure (MOE) of 10 to 1,000 based on a range of exposure levels (0.01 to 1 mg/kg bw/day) and the lowest dose levels in animal studies that caused suppressed immune function (10 mg/kg bw/day).
<b>Other information</b> No other information.

## 26. What is your Level of Concern for adults in the general population?

<b>Hazard: Suspected</b>
<p><b>Human evidence: <i>Low evidence</i></b></p> <p>A study of community members exposed via the drinking water following a chemical spill showed some effects on inflammatory mediators (e.g., cytokines, histamine, bradykinin, etc.). There is additional evidence for effects in highly exposed occupational populations. The level of evidence was downgraded from high to low because the studies did not have controlled exposure (i.e., they were observational in design rather than randomized control trials) and for indirectness (use of an inflammation mediator as a surrogate for an immunological effect).</p>
<p><b>Animal evidence: <i>High evidence</i></b></p> <p>Numerous studies in rodents indicate that several chemicals in this class of compounds suppress immune function. The effect of suppressed immune function occurred following adult and/or developmental exposures at dose levels ranging from 10 to 100 mg/kg bw/day.</p>
<p><b>Mechanistic/other evidence</b></p> <p>Lowers the hazard identification classification from "presumed" to "suspected." Mechanistic evidence suggest the pathways associated with immunotoxicity in rodents are not applicable to humans. In addition, the chemicals in this class have a much longer half-life in rodents compared to humans.</p>
<b>Exposure</b>
<p><b>Exposure description</b></p> <p>Exposure can occur from a variety of consumer products including cookware, stain resistant fabrics, textiles, and carpet. Some members of this chemical class were voluntarily phased out and are being replaced by others with similar structures.</p> <p>Margin of Exposure (MOE) of 100 to 1,000 based on a range of exposure levels (0.01 to 0.1 mg/kg bw/day) and the lowest dose levels in animal studies that caused suppressed immune function (10 mg/kg bw/day).</p>
<p><b>Other information</b></p> <p>No other information.</p>

## 27. What is your Level of Concern for workers at the current regulatory limit of 1 ppm?

<b>Hazard: Presumed</b>
<p><b>Human evidence: <i>Inadequate evidence</i></b></p> <p>No studies available.</p>
<p><b>Animal evidence: <i>High evidence</i></b></p> <p>Inhalation exposure to rats (125, 250, or 500 ppm) caused dose-related increases in tumors of the large intestine (a very rare tumor) in females, and skin tumors in males at <math>\leq 125</math> ppm. Inhalation exposure to mice (62.5, 125, or 250 ppm) was associated with dose-related increases of skin tumors in both sexes (<math>\leq 62.5</math> ppm).</p>
<p><b>Mechanistic/other evidence</b></p> <p>No impact on hazard identification classification.</p>
<b>Exposure</b>
<p><b>Exposure description</b></p> <p>Exposure levels vary by industry. The time-weighted average (TWA) daily exposure varies among industries with reported air concentrations, ranging from 25 to 175 ppm.</p> <p>Margin of Exposure (MOE) of <math>&lt;1</math> to 2.5 based on a range of exposure levels (25 to 175 ppm) and the lowest dose levels in animal studies that caused a significant increase in tumors (62.5 ppm).</p>
<p><b>Other information</b></p> <p>High productive volume chemical.</p>

## 28. What is your Level of Concern for workers?

<b>Hazard: Known</b>
<p><b>Human evidence: <i>Moderate evidence</i></b></p> <p>Several occupational cohort studies found a positive association with lymphohematopoietic cancers, especially those with lymphoid cell origin. The strongest evidence comes primarily from a large cohort study showing an association of these types of cancer with cumulative exposure in men. Cumulative exposure is also associated with breast cancer in women. The level of evidence was considered moderate based on downgrades for studies not having a controlled exposure (i.e., they were observational in design rather than randomized control trials) and concern for risk of bias with respect to confounding; however, there was also an upgrade based on evidence of a dose-gradient.</p>
<p><b>Animal evidence: <i>High evidence</i></b></p> <p>Inhalation exposure caused dose-related increases in brain tumors (<math>\geq 100</math> ppm), mononuclear-cell leukemia (<math>\geq 50</math> ppm), peritoneal mesotheliomas (<math>\geq 100</math> ppm) or subcutaneous fibroma (<math>\geq 100</math> ppm) and tumors of the lung (<math>\geq 100</math> ppm), and tumors of the harderian gland (<math>\geq 50</math> ppm), uterus, and mammary gland (<math>\geq 50</math> ppm) in mice. Local tumors were also observed in rats exposed by gavage (forestomach tumors at 750 mg/kg bw/day) and mice exposed by subcutaneous injection (sarcoma at 100 mg/kg bw/day).</p>
<p><b>Mechanistic/other evidence</b></p> <p>Raises the hazard identification classification from "presumed" to "known." The chemical has been shown to cause chromosomal damage in mammalian cells and is mutagenic in bacterial cells.</p>
<b>Exposure</b>
<p><b>Exposure description</b></p> <p>Average exposure is 1 to 2 ppm in most jobs and up to 5 ppm for "highest exposed" since the late 1970s; probably higher in earlier years.</p> <p>Margin of Exposure (MOE) of <math>\sim 10</math> to 50 based on a range of exposure levels (1 to 5 ppm) and the lowest dose levels in animal studies that caused a significant increase in tumors (50 ppm).</p>
<p><b>Other information</b></p> <p>High productive volume chemical.</p>

## 29. What is your Level of Concern for general population?

<b>Hazard: Presumed</b>
<p><b>Human evidence: <i>Inadequate evidence</i></b></p> <p>No studies available.</p>
<p><b>Animal evidence: <i>Moderate evidence</i></b></p> <p>Adrenal hypertrophy was observed in Sprague-Dawley rats exposed to 0.92 or 1.8 mg/kg bw/day in drinking water for 30 days; corticosterone levels were reduced and stimulated ACTH response was significantly greater. Decreased adrenal gland weight was reported in female Wistar rats exposed to 8 mg/kg bw/day via drinking water for 90 days and in male Sprague-Dawley rats exposed to 8 mg/kg bw/day via drinking water for 24 weeks. The level of evidence was downgraded from high to moderate based on concern for risk of bias (internal validity).</p>
<p><b>Mechanistic/other evidence</b></p> <p>Raises the hazard ID categorization identification from "suspected" to "presumed." Raises hazard identification; mechanistic data shows the chemical inhibits enzymes required for corticosteroid synthesis</p>
<b>Exposure</b>
<p><b>Exposure description</b></p> <p>No data available on human exposure levels.</p> <p>Margin of Exposure (MOE) is unknown.</p>
<p><b>Other information</b></p> <p>Chemical is listed as an ingredient in cosmetics and certain household products.</p>

## 30. What is your Level of Concern for male workers?

<b>Hazard: Known</b>
<p><b>Human evidence: High evidence</b></p> <p>A very large number of epidemiological studies, including prospective cohort studies, have documented associations between exposure and lower IQ in children; there is evidence of a dose gradient. These studies have been summarized and evaluated in numerous government risk assessments. Public health actions are recommended when children have blood levels above 5 µg/dL.</p>
<p><b>Animal evidence: Inadequate evidence</b></p> <p>No studies available.</p>
<p><b>Mechanistic/other evidence</b></p> <p>No impact on hazard identification classification.</p>
<b>Exposure</b>
<p><b>Exposure description</b></p> <p>Blood levels in workers range from 10 to 25 µg/dL.</p> <p>Blood levels in workers exceed blood levels in pregnant women or children associated with IQ deficits.</p>
<p><b>Other information</b></p> <p>No other information.</p>

## 31. What is your Level of Concern for male workers?

<b>Hazard: Known</b>
<p><b>Human evidence: Low evidence</b></p> <p>Men occupationally exposed had some changes in testicular endocrine function, as measured by serum levels of reduced testosterone, luteinizing hormone (LH), and follicle stimulating hormone (FSH). The level of evidence was considered low based on downgrades because the study did not have controlled exposure (i.e., observational in design rather than randomized control trials) and for indirectness (use of hormone alterations as an indicator of reproductive toxicity).</p>
<p><b>Animal evidence: High evidence</b></p> <p>Reproductive toxicity has been evaluated in two rat studies and two mouse studies. In one study, adult male Sprague-Dawley rats treated via inhalation at 70 ppm for 70 days (a single dose level study) had lower testicular weights and numerous histological abnormalities in the seminiferous tubules. In a second study, adult male Fisher rats treated with 50 ppm via inhalation for 3 months had lower testis and caput epididymis weights, lower serum luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels, and reduced fertility compared to controls. Adult male mice treated by inhalation for 10 consecutive days with 625, 1250, 2500, or 5000 ppm had lower sperm counts at all dose levels, and testes weights were lower at ≥2500 ppm. In the second mouse study, males were treated by inhalation for 5 consecutive days with 0, 25, 50, 100, 200, 400, or 500 ppm. Testis weights and sperm counts were significantly lower than controls at doses ≥50 ppm.</p>
<p><b>Mechanistic/other evidence</b></p> <p>Raises the hazard ID categorization identification from "presumed" to "known." The chemical is an anti-androgen.</p>
<b>Exposure</b>
<p><b>Exposure description</b></p> <p>Occupational exposure is typically 0.1 to 0.5 ppm (time weight average).</p> <p>Margin of Exposure (MOE) of ~100 to 500 based on a range of exposure levels (0.1 to 0.5 ppm) and the lowest dose levels in animal studies that caused reproductive toxicity (50 ppm).</p>
<p><b>Other information</b></p> <p>No other information.</p>

## 32. What is your Level of Concern for women of reproductive age?

<b>Hazard: Suspected</b>
<p><b>Human evidence: Moderate evidence</b></p> <p>Significant associations were observed for longer time to pregnancy in 2 prospective studies. A cross-sectional study identified an association with self-report of irregular menstrual cycles. The level of evidence for the prospective studies was considered moderate based on a downgrade for studies not having a controlled exposure (i.e., they were observational in design rather than randomized control trials).</p>
<p><b>Animal evidence: Low evidence</b></p> <p>Oral exposure of rats to <math>\geq 0.100</math> mg/kg bw/day for 10 weeks decreased litter size, increased ovarian follicular cysts, and increased estrous cycle length in females. The level of evidence was downgraded from high to low based on (1) concern for risk of bias (internal validity), and (2) unexplained inconsistency with two other studies in rats of similar design that reported effects at similar dose levels.</p>
<p><b>Mechanistic/other evidence</b></p> <p>No impact on hazard identification classification.</p>
<b>Exposure</b>
<p><b>Exposure description</b></p> <p>Exposure of the general population is estimated at 0.001 mg/kg bw/day.</p> <p>Margin of Exposure (MOE) of <math>\sim 100</math> based on estimated daily intake of 0.001 mg/kg bw/day and the lowest dose levels in animal studies that caused reproductive toxicity (0.1 mg/kg bw/day).</p>
<p><b>Other information</b></p> <p>High productive volume chemical.</p>

## 33. What is your Level of Concern for workers?

<b>Hazard: Known</b>
<p><b>Human evidence: High evidence</b></p> <p>The kidney is considered one of the main target organ of toxicity following extended inhalation exposure. The sensitivity of the kidney was initially recognized in a 1950 investigation of workers exposed to fumes in a factory setting. These workers suffered from a high incidence of abnormal renal function, indicated by proteinuria and a decrease in glomerular filtration rate. Over 20 other studies in workers have reported various effects on the kidneys. Associations with decreased glomerular filtration rate have been reported at blood levels <math>\geq 8.4 \mu\text{g/L}</math>.</p>
<p><b>Animal evidence: Moderate evidence</b></p> <p>In rats, moderate to severe degenerative changes in the renal tubular epithelium were observed following inhalation treatment with 3 ppm for 3 hours a day, 5 days a week for 12–42 weeks. Rabbits treated via inhalation with 0.86 ppm for 7 hours a day, 5 days a week for 12 weeks exhibited moderate pathological kidney changes that were reversible with cessation of exposure. Larger doses (6 ppm) administered to rabbits for 7 hours a day, 5 days a week, for up to 11 weeks, produced effects that ranged from mild, unspecified, pathological changes to marked cellular degeneration and widespread necrosis. The level of evidence was downgraded from high to moderate based on concern for risk of bias (internal validity).</p>
<p><b>Mechanistic/other evidence</b></p> <p>No impact on hazard identification classification.</p>
<b>Exposure</b>
<p><b>Exposure description</b></p> <p>Occupational exposure is typically 0.05 to 0.01 ppm (time weight average).</p> <p>Margin of Exposure (MOE) of <math>\sim 17</math> to 86 based on a range of exposure levels (0.05 to 0.01 ppm) and the lowest dose levels in animal studies that caused kidney effects (0.86 ppm).</p>
<p><b>Other information</b></p> <p>No other information.</p>

## 34. What is your Level of Concern for adult males?

<b>Hazard: Not classifiable</b>
<b>Human evidence: <i>Inadequate evidence</i></b> No studies available.
<b>Animal evidence: <i>Low evidence</i></b> Developmental neurotoxicity was reported in a collection of rat and mouse studies at oral doses ranging from 20 to 80 mg/kg bw/day (either to the dam or directly to offspring after weaning). The studies reported effects on different aspects of neurotoxicity, including learning and memory and reflex development. The level of evidence was downgraded from high to low based on concern for (1) risk of bias (internal validity) and (2) publication bias.
<b>Mechanistic/other evidence</b> No impact on hazard identification classification.
<b>Exposure</b>
<b>Exposure description</b> Exposure of the general population is estimated at 0.2 mg/kg bw/day.  Margin of Exposure (MOE) of ~100 based on estimated daily intake of 0.2 mg/kg bw/day and the lowest dose levels in animal studies that caused reproductive toxicity (20 mg/kg bw/day).
<b>Other information</b> No other information.

## 35. What is your Level of Concern for general population?

<b>Hazard: Suspected</b>
<b>Human evidence: <i>Inadequate evidence</i></b> No studies available.
<b>Animal evidence: <i>High evidence</i></b> Many studies in laboratory animals have reported effects on the thyroid. Reported findings have included reduced thyroid iodide uptake, increased levels of iodide in serum, decreased serum thyroxine (T4) and triiodothyronine (T3), increased serum thyroid stimulating hormone (TSH), increased thyroid size and weight, and hypertrophy and hyperplasia of thyroid cells, eventually leading to fibrosis and tumor development. Doses reported to produce these effects ranged from 7 to 3,811 mg/kg bw/day after exposure durations ranging from 1 day to 2 years.
<b>Mechanistic/other evidence</b> Lowers the hazard ID categorization identification from "presumed" to "suspected." Thyroid effects are attributed to accumulation of a metabolite that is not produced in humans.
<b>Exposure</b>
<b>Exposure description</b> Exposure of the general population is estimated at 0.07 mg/kg bw/day.  Margin of Exposure (MOE) of ~100 based on estimated daily intake of 0.07 mg/kg bw/day and the lowest dose levels in animal studies that caused thyroid effects (7 mg/kg bw/day).
<b>Other information</b> No other information.

## 36. What is your Level of Concern for people taking this drug?

<b>Hazard: Not classifiable</b>
<p><b>Human evidence: <i>Low evidence</i></b></p> <p>In four case reports, the effect of treatment with this drug on muscle coordination was reported. In one case, there was no effect on muscle coordination. In three cases, impaired muscle coordination was reported. In all three of these cases, muscle function returned to normal 3 to 12 months following discontinuation of treatment. The level of evidence was considered low based on a downgrade for studies being case reports (no reference group, small sample size).</p>
<p><b>Animal evidence: <i>Low evidence</i></b></p> <p>Oral treatment of rats to <math>\geq 1</math> mg/kg bw/day for 10 weeks caused ataxia. The level of evidence was downgraded from high to low based on (1) concern for risk of bias (internal validity) and (2) unexplained inconsistency with two other studies in rats of similar design that reported effects at similar dose levels.</p>
<p><b>Mechanistic/other evidence</b></p> <p>No impact on hazard identification classification.</p>
<b>Exposure</b>
<p><b>Exposure description</b></p> <p>The typical therapeutic dose is 5 mg/kg bw/day.</p> <p>Margin of Exposure (MOE) of <math>&lt;1</math> based on therapeutic dose (5 mg/kg bw/day) and the lowest dose level in the animal study where ataxia was reported (1 mg/kg bw/day).</p>
<p><b>Other information</b></p> <p>No other information.</p>

## 37. What is your Level of Concern for infants and children with relatively high exposure via the diet?

<b>Hazard: Suspected</b>
<p><b>Human evidence: <i>Inadequate evidence</i></b></p> <p>No studies available.</p>
<p><b>Animal evidence: <i>Moderate evidence</i></b></p> <p>Numerous studies in rodents and primates indicate that several chemicals in this class of compounds suppress immune function. This effect of suppressed immune function occurred following adult and/or developmental exposures at dose levels ranging from 10 to 100 mg/kg bw/day. The level of evidence was downgraded from high to moderate based on concern for risk of bias (internal validity).</p>
<p><b>Mechanistic/other evidence</b></p> <p>No impact on hazard identification classification.</p>
<b>Exposure</b>
<p><b>Exposure description</b></p> <p>Intake in population with relatively high exposure via the diet is estimated at <math>\sim 1</math> mg/kg bw/day. Other findings reported in general population with estimated exposure of 0.01 mg/kg bw/day.</p> <p>Margin of Exposure (MOE) of 10 to 1,000 based on a range of exposure levels (0.01 to 1 mg/kg bw/day) and the lowest dose levels in animal studies that caused suppressed immune function (10 mg/kg bw/day).</p>
<p><b>Other information</b></p> <p>No other information.</p>

## 38. What is your Level of Concern for workers?

<b>Hazard: Suspected</b>
<p><b>Human evidence: <i>Low evidence</i></b></p> <p>Men occupationally exposed had elevations in the liver enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT). The level of evidence was considered low based on downgrades for the study not having a controlled exposure (i.e., observational in design rather than randomized control trials) and for indirectness (more detailed analysis of liver function was not conducted or reported).</p>
<p><b>Animal evidence: <i>Low evidence</i></b></p> <p>Oral exposure to mice at <math>\geq 1</math> mg/kg bw/day resulted in altered liver gene expression (but no impacts on weight or liver enzyme levels) in one of three studies of very similar design. The level of evidence was downgraded from high to low based on (1) indirectness (unclear biological significance of the changes in gene expression) and (2) unexplained inconsistency with two other studies in rats of similar design that reported effects at similar dose levels.</p>
<p><b>Mechanistic/other evidence</b></p> <p>Raises the hazard ID categorization identification from "not classifiable" to "suspected." The chemical is positive in several in vitro models used to assess liver toxicity.</p>
<b>Exposure</b>
<p><b>Exposure description</b></p> <p>Occupational exposures are typically 0.5 to 0.1 mg/kg bw/day.</p> <p>Margin of Exposure (MOE) of ~5 to 10 based on a range of exposure levels (0.1 to 0.2 mg/kg bw/day) and the lowest dose levels in animal studies that caused gene expression changes in the liver (1 mg/kg bw/day).</p>
<p><b>Other information</b></p> <p>No other information.</p>

## 39. What is your Level of Concern for infants and children in the general population?

<b>Hazard: Suspected</b>
<p><b>Human evidence: <i>Low evidence</i></b></p> <p>Several epidemiological studies in children have shown increased risk for respiratory disease and otitis media, and reduced efficacy of vaccination. The level of evidence was downgraded from high to low because the studies (1) did not have controlled exposure (i.e., they were observational in design rather than randomized control trials) and (2) they were cross-sectional in design and did not allow a determination of whether exposure preceded outcome assessment.</p>
<p><b>Animal evidence: <i>Moderate evidence</i></b></p> <p>Numerous studies in rodents and primates indicate that several chemicals in this class of compounds suppress immune function. The effect of suppressed immune function occurred following adult and/or developmental exposures at dose levels ranging from 10 to 100 mg/kg bw/day. The level of evidence was downgraded from high to moderate based on concern for risk of bias (internal validity).</p>
<p><b>Mechanistic/other evidence</b></p> <p>No impact on hazard identification classification.</p>
<b>Exposure</b>
<p><b>Exposure description</b></p> <p>Exposure of the general population is estimated at 0.01 mg/kg bw/day.</p> <p>Margin of Exposure (MOE) of 1,000 based on general population exposure levels (0.01 mg/kg bw/day) and lowest dose levels in animal studies that caused suppressed immune function (10 mg/kg bw/day).</p>
<p><b>Other information</b></p> <p>No other information.</p>

## 40. What is your Level of Concern for general population?

<b>Hazard: Presumed</b>
<p><b>Human evidence: <i>Moderate evidence</i></b>  A relative risk (95% CI) of 1.23 (1.15 to 1.31) was reported based on a meta-analysis of 10 occupational studies (and 1,082 participants) that evaluated myocardial infarction. The level of evidence was considered moderate based on a downgrade for the study not having a controlled exposure (i.e., observational in design rather than randomized control trials).</p>
<p><b>Animal evidence: <i>Moderate evidence</i></b>  Dose-related cardiomyopathy was observed in a 6-month study in Sprague-Dawley rats where males and females were treated via the diet with ~175, 350, 700, and 1000 mg/kg bw/day. Statistically significant findings of cardiomyopathy were observed at ≥350 mg/kg bw/day. The level of evidence was downgraded from high to moderate based on concern for risk of bias (internal validity).</p>
<p><b>Mechanistic/other evidence</b>  No impact on hazard identification classification.</p>
<b>Exposure</b>
<p><b>Exposure description</b>  Exposure of the general population is estimated to be ~0.001 mg/kg bw/day.</p> <p>Margin of Exposure (MOE) of 350,000 based on general population exposure levels (0.001 mg/kg bw/day) and lowest dose levels in animal studies that caused cardiomyopathy (≥350 mg/kg bw/day).</p>
<p><b>Other information</b>  No other information.</p>