Version 2 1,3-butadiene

Short report from Danish Working Environment Authority´s (AT) Occupational exposure limit quality committee. Evaluation of the report: 1,3-butadiene: Scientific basis for setting a health-based occupational exposure limit

Members of the quality committee: Nellie Anne Martin (Miljøstyrelsen); Anoop Kumar Sharma (DTU Fødevareinstituttet); Mette Lausten Hansen, (Arbejdsmedicin AUH); Jesper Bo Nielsen (Institut for Sundhedstjenesteforskning, SDU); Vivi Schlünssen (NFA)

This report is based on an online meeting 17th December 2021 headed by AT, where the results from the report were discussed after the authors presented the content of the report. The members of the quality committee had the chance to ask questions to the authors.

The Report: Pernille Høgh Danielsen, Anne Thoustrup Saber, Niels Hadrup, Nicklas Raun Jacobsen, Sarah Søs Poulsen, Karin Sørig Hougaard, Ulla Vogel. Evaluation of the report: 1,3-butadiene: Scientific basis for setting a health-based occupational exposure limit. The National Research Centre for the Working Environment (NFA), Copenhagen 2021. ISBN 978-87-7904-377-0

Erratum: The heading for table 5 should be corrected to: "Relative risk of mortality".

Response: corrected in the revised report.

An overview of abbreviations would be helpful

Response: A list of abbreviation used is included in the revised report.

Table 11. It is unexpected BMDL10 is lower (1) than BMCL05 (2.2). What is the difference between BMDL and BMCL?

Response: BMDL10 and BMCL05 derived by DECOS and OEHHA, respectively, are different because they use different approaches, albeit the same Benchmark Dose Software (version 2.3.0 and 2.1.2, respectively). The approaches are different since DECOS used the ovarian atrophy data from 103 weeks of exposure as point of departure, whereas OEHHA used the full data sets of 9, 15, and 24 months of exposure as their basis for the deviation. Other differences are possible, but it is difficult to compare 1:1, because the level of detail in reporting differs considerably between the two – OEHHA are very detailed about their approach compared to DECOS that supply far less detail.

We have added this as a note to Table 11.

Page 32, last line. Atophy should be corrected to atrophy.

Response: Corrected in the revised report.

Overall evaluation of the report

This well written report reviews data relevant to assessing the hazards of 1,3-butadiene in humans and in animals. Furthermore, toxicokinetics and mechanisms of (geno)toxicity are briefly reviewed, and previous risk assessments of 1,3-butadiene are summarized. The scientific basis for setting an occupational exposure limit (OEL) are presented including both non-threshold effects (cancer (leukaemia)) and threshold effects (reproductive toxicity (ovarian atrophy)).

For non-threshold effect the authors assess an excess cancer risk (based on mortality data (leukaemia) from one recently updated cohort) to be 1:1,000 at 3.1 mg/m3, 1:10,000 at 0.31 mg/m3 and 1: 100,000 at 0.031mg/m3 1,3-butadiene. The authors also assessed excess cancer risk based on incident mice data (lymphoma), and found a similar excess cancer risk (e.g. 1:1,000 at 1.556 mg/m3).

For threshold effects the authors, based on one mice study, suggest a DNEL (Derived No-Effect Level) equal to 0.138 mg/m3.

The authors widely rely on existing previous risk assessments of 1,3-butadiene updated with a new Pubmed search from 2010 - 2020. This is clearly stated in the introduction and the committee agrees with the approach but suggests to add a statement (disclaimer) about the implications of this choice (use of conclusions from existing sources, critical appraisal limited). The search resulted in

831 publications, narrowed down to 92 references of potential relevance for the report. It is stated: "Of these, only some were relevant for inclusion in the report". The committee suggest to include the exact number in the report. There is no information about the search string in the report. In order to make a comprehensive search, the authors could have considered broaden the search to other databases, for example Scifinder.

Response:

- Disclaimer statement – our search strategy matches the one suggested by DECOS in a new guidance document "Guidance for recommending classifications and health-based occupational exposure limits", December 2021. *"The search starts with the search for reports that were published by other scientific organizations"*, such as DECOS, SCOEL, IARC, and ECHA. *"If such reports are available, the literature search starts at the last date of the search mentioned in the relevant assessment report"*. In this case, we started the literature search from year 2010 with a small overlap in the time interval covered with the 1,3-butadiene report from DECOS which was published in 2013.
We have added a bit more details to the present report covering these aspects and furthermore add the following disclaimer statement: "We put weight on other scientific organizations reports and their conclusions, although not uncritically. Furthermore, our critical appraisal was limited to original literature published after 2010".
- Exact number – 16 of the 92 publications are cited in the present report. Due to the search overlap in time, five publications out of the 92 were included in the report by DECOS, but were not cited in the present report. This is now clearly stated in the report.
- Other databases – We agree that searching additional databases would broaden the search and potentially increase literature findings. We will consider this in our future reports, however, which database will depend on the institutional availability at NFA.

The authors focus on studies dealing with occupational exposure by inhalation, and the committee support that decision, as inhalation is probably the major route of exposure for 1,3-butadiene due to the low boiling point..

There is no information about 1,3-butadiene levels in the Danish working population. We assume this is because no measurements from Denmark is available. It would be of relevance to include an estimate of numbers of exposed workers in Denmark. The authors could consider to include

information provided in "Proposal for a Directive of the European Parliament and of the Council amending Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens or mutagens at work" (page 148).

Response: We have now included a sentence about the number of exposed workers in DK (page x in the revised report), which is 422 workers according to table 4, page 138 in "Proposal for a Directive of the European Parliament and of the Council amending Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens or mutagens at work".

On page 17 (Toxicokinetics) there is a section on genetic variation. Does the statement "The specific impact of these polymorphisms is not completely known, but it likely involves complex interactions. In vitro studies and in vivo molecular epidemiological studies indicate the range of increased sensitivity that may be attributed to some human genetic polymorphisms is approximately 2- to 3.5-fold in humans as a worst-case scenario" refer to 1,3-butadiene – or is it a more overall statement?

Response: This statement refers to 1,3-butadiene (the reference for this statement is incorrect in the original version of our report, we have changed it to the correct one (Kirman et al. 2012)).

Regarding animal studies it seem to be justified that mice produce significantly more epoxide metabolites – 2 orders of magnitude is mentioned (page 18, Kirman et al 2010), and therefore potentially are more susceptible to 1,3-butadiene exposure compared to humans, which challenges the validity of animal models based on mice for the study of 1,3-butadiene. Still, mice studies are used in the present report to evaluate both non-threshold and threshold effects in animals. The committee are aware most data originate from mice studies (though, in contrary to mice, rats did not develop ovarian atrophy after exposure to comparable levels in (Doerr et al 1996). We suggest the authors to include a section in the report where they more explicitly touch upon this limitation in the animal (mice) studies.

Response:

The following section describing metabolic species differences related to ovarian toxicity is added to the revised report in the section 'Reproductive toxicity':

"Regarding interspecies variation, data suggest significant differences in the sensitivity to 1,3-butadiene between mice and rats, which are partly due to the metabolic differences between species. Differences in the formation rate and detoxification of epoxide metabolites have been observed, in

terms of higher tissue levels of epoxide metabolites in rodents, predominantly in mice, than in humans. For example, in vitro and perfusion data show that mice are more efficient than rats at oxidizing 1,3-butadiene to form EB, and that the conversion of EB to DEB in mice is 3.3-fold greater than in rats and 2.4–61-fold greater than in humans (Kirman et al. 2010). In addition, in vitro studies designed to assess interspecies differences in the activation of 1,3-butadiene and inactivation of epoxides revealed that the overall activation/detoxication ratio for metabolism was approximately 10 times higher in mice compared to that of rats or humans (Bond et al. 1993). Biomarkers of exposure have been identified for the epoxide metabolites including pyr-Val hemoglobin adducts, which have shown a good surrogate biomarker for DEB (Georgieva et al 2010). DEB is the metabolite with the highest genotoxic potency and the metabolite suggested being the causative agent for ovarian atrophy (NTP 1993, Kirman et al. 2012). The DEB dose-equivalent in human blood (measured as pyr-Val hemoglobin adducts) was shown to be approximately 16 times lower than in rats, which in turn was approximately 45 times lower than the DEB blood levels in mice (Swenberg et al. 2011). Thus there is a 720-fold difference between mice and humans. Furthermore, follicle cell depletion has been observed in mice following short-term exposures (30-day) to EB and DEB, and in rats following short-term exposures to DEB (Doerr et al., 1996).

The current working group consider the human cohort data to be the most appropriate data for evaluating the non-threshold effects (leukemia mortality) which are included in table 11 in conclusion. We included the section with calculations based on the mouse studies (lymphoma incidence) for comparative reasons.

Regarding, the threshold effects based on ovarian atrophy in mice, it is the current working group's opinion, that it is very important to note: 1) we do take the interspecies metabolic differences into consideration in our calculation of a DNEL by setting the interspecies extrapolation factor to 1 (the appropriate setting of the uncertainty level can of course be discussed); 2) there are other uncertainties, that we do not take into consideration in the calculations, such as inherent genetic susceptibilities affecting the metabolic pathway, the individual variation in follicle reserves, that the size of the follicle reserve decreases with age, and that smokers would be exposed to 1,3-butadiene from cigarette smoke in addition to the occupational exposure. In the calculation of DNEL, we used the approach by ECHA, where the intra-species factor is set to 5 as a default value for workers.

NFA notes that for ovarian effects in mice, the point of departure is a LOAEL, and that the endpoints assessed, i.e. ovarian atrophy with complete depletion of follicles, represent the final state of ovary degeneration. Hence, much less histologically apparent adverse effects (i.e. gradual decrease in follicle number) may have occurred at lower exposure levels and could have resulted in reduced fertility. Follicle cell depletion has been observed both in mice and rats following short-term exposures (30-day) to DEB (Doerr et al., 1996). Rats did not develop ovarian atrophy after exposure to 1,3-butadiene (Owen et al. 1987), but they could potentially have had decreased numbers of follicles (to the best of our knowledge this was not assessed).

NFA notes that there may be important inter-species differences in fertility between mice and women, and that Danish women on average give birth to their first child at 29 years of age, where they are already subject to age-related decline in ovarian follicles.

NFA notes that for other threshold effects, including inflammation and acute phase response, linear correlations have been found in epidemiological studies at exposure concentrations well below the threshold that was defined based on animal studies. Infertility is a severe adverse effect, which will affect ca 2/3 of the average lifespan (when the women live without having achieved desired children due to infertility).

Hence, the uncertainty related to establishment of a threshold effect should be carefully considered.

We have added a calculation of a health-based exposure limit based on ovarian atrophy in mice to the revised report taking these uncertainties into account alongside the ECHA approach.

We assume in the following that ovarian atrophy is mediated by the formation of DEP based on evidence from the existing literature (Kirman et al. 2012). The interspecies difference between humans and mice is 720-fold in DEP blood levels following metabolism of 1,3-butadiene (Swenberg et al. 2011).

Below we argue for the used assessment factors in this addition:

Use of LOAEL instead of a NOAEL: 10 (the highest factor due to the complete depletion of follicles in mice).

The following assessment factors (intraspecies) are included (rather than the default value from ECHA):

$LOAEL_{corr} = 6.9$ mg/m^3

Calculation of $DNEL_{NFA}$: 6.9 mg/m^3 / (10*8.5*3*3*2*10*3) = 0.00015 mg/m^3

We then multiply with 720 reflecting the difference in DEP levels between mice and humans:

$DNEL_{NFA}$: 0.00015 mg/m^3 x 720 = 0.108 mg/m^3 = 108 µg/m^3

This calculation, where we take the difference in DEB blood levels between humans and mice as well as important uncertainty factors into account, results in a DNEL similar to the DNEL calculated in the original report when using the approach recommended by ECHA.

Hence, the current working group has the opinion that as long as we do not have clear evidence that ovarian atrophy is an irrelevant end point for humans exposed to potentially high levels of 1,3-butadiene in occupational settings, the precautionary principle should come into force when dealing with adverse effects related to the reproductive system.

Page 22, mechanisms of toxicity. Mutagenicity and genotoxicity are described as quotes from IARC 2008, 2012 and Kirman et al 2010. In order to evaluate the results the committee request more detailed information, including a brief summary of types of media (e.g. blood, urine), type of test (e.g. DNA adducts, comet assay, clastogenicity etc). What is the evidence in animals, e.g. some details about metabolites assessed in animals would be helpful (for instance studies that have tested both 1,3 butadiene and metabolites/DEB).

Response:

We have extended the section 'Mutagenicity and genotoxicity' with more detailed information.

IARC extensively reviewed the available literature on mutagenicity and genotoxicity in their 2008 report. At that time, the literature consisted of 54 scientific publications on 1,3-butadiene exposure to different experimental test systems, 18 publications on the metabolite epoxybutene (EB), 4 publications on the metabolite epoxybutanediol (EBD) and 22 publications on the metabolite diepoxybutane (DEB) to different test systems. The most common test systems are:

-*Salmonella typhimurium* or *E.coli* reverse mutation

-DNA cross-links *in vivo*

-DNA single-strand breaks *in vivo*

-Sister chromatid exchange *in vitro* (rodent or human whole blood, rodent fibroblasts)

-Gene mutations (*LacI*/ *Hprt* locus *in vivo* or *Hprt* locus in human lymphoblastoid TK6 cells)

-Micronucleus formation *in vivo* (liver/ lung) or *in vitro* (rodent fibroblasts)

-Chromosomal aberrations *in vivo*

-Dominant lethal test

-Binding to DNA at N7 of guanine *in vivo* (various tissues).

Less common test systems are cell cycle arrest, hyperdiploidy, chromosomal breakage, inhibition of clonogenic activity, aneuploidy and comet tail moment.

Generally, the metabolites have been investigated to a minor extent *in vivo* compared to *in vitro* test systems.

A few publications have assessed the same end point simultaneously for both 1,3-butadiene and metabolites. The effects can be difficult to compare across studies due to differences in exposure concentrations, exposure duration or administration method. Three studies were described in the IARC report:

1) Recio et al. 2001. Male lacI mice were exposed to BD by whole-body inhalation (62.5 ppm, 625 ppm or 1250 ppm for 6 h/day) and female lacI mice were exposed to EB and DEB (29.9 ppm for 2

weeks and 3.8 ppm for 2 weeks, respectively). Conclusion: *The data presented clearly indicate that BD exposure induces specific point mutations in tissues of lacI mice and that EB and DEB differ in the mechanisms by which they induce mutation in mammalian cells. In the experimental systems examined, EB primarily acts via the induction of point mutations, while DEB induces point mutations, deletions, and chromosomal alterations. In mice exposed to BD, both metabolites and EBD may act in concert to induce the range of genotoxicity observed.*

2) Walker & Meng 2000 (only abstract available at NFA). *The relative contribution of BDO* (EB) *versus BDO2* (DEB) *to overall BD mutagenicity was evaluated by exposing mice and rats to carefully chosen concentrations of BD and racemic mixtures of BDO and BDO2 (that is, 62.5, 2.5, and 4.0 ppm, respectively) and comparing the mutagenic potency of each compound when comparable blood levels of metabolites were achieved. The resulting MF* (mutant frequency) *data indicate that (+/-)-BDO2 is a major contributor to the mutagenicity of BD in mice at lower BD exposure levels (< or = 62.5 ppm).*

3) Wickliffe 2007. Knockout mice (Ephx1-null and Xpc-null) were exposed either to BD by inhalation or to the reactive epoxide metabolites, EB or DEB by intraperitoneal injection. The doses were 20 ppm (7h/day, 5 days/week for 4 weeks) of BD by inhalation or ED (Ephx1-null: 240 mg/kg (three separate injections of 80 mg/kg every 48 h); Xpc-null: 300 mg/kg (three separate injections of 100 mg/kg every 48 h)) or DEB (Ephx1-null: 30 mg/kg (two separate injections of 15 mg/kg every 24 h). The EPHX gene codes for the detoxification enzyme epoxide hydrolase and the XPC gene is involved in nucleotide excision repair mechanisms. Genetic susceptibility was measured using the Hprt cloning assay measuring mutant frequencies. Conclusion: *Both deficient strains of mouse were significantly more sensitive to the mutagenic effects of BD and the injected epoxides, which indicate that individuals deficient in both hydrolytic detoxification and repair of premutagenic DNA adducts may be at a particularly high risk following exposure to BD.*

The evidence for mutagenicity and genotoxicity in humans has been investigated in workers in styrene-butadiene or butadiene monomer facilities. Effects have been assessed in workers exposed to 1,3-butadiene and control groups as e.g. HPRT variant (mutant) frequency in lymphocytes, concentration of urinary metabolite of butadiene, chromosomal aberrations and sister chromatid exchange in blood cells, and DNA adducts in lymphocytes. However, there are also studies showing conflicting results in the literature (reviewed by IARC).

Page 23, epigenetic changes. Is there any information about 1,3-butadiene metabolites (most importantly DEB), or does the epigenetic papers only investigate 1,3-butadiene as such?

Response: Experiments assessing epigenetic changes are only performed in animals exposed to 1,3-butadiene by inhalation.

Page 25, DECOS (2013). The authors cite DECOS's reflections about leaving DMDTC out of the models used to assess dose-response relations (risk for over-adjustment) which is a valid argument. But why are the other covariates not taken into consideration in the models used in (Chen et al. 2007; Sathiakumar et al. 2015) e.g. ethnicity, plant, year since hire etc.)

Response: Unfortunately, we do not know why DECOS made this choice, as we write, *"DECOS does not explain this choice in their report"* on page 25. Thus, to come up with an explanation would be speculation from our side.

Scientific bases for an occupational exposure limit for RCS

For non-threshold effect the authors assess an excess cancer risk (based on mortality data (leukaemia) from one recently updated cohort) to be 1:1,000 at 3.1 mg/m3, 1:10,000 at 0.31 mg/m3 and 1: 100,000 at 0.031mg/m3 1,3-butadiene. The authors also assessed excess cancer risk based on incident mice data (lymphoma), and found a similar excess cancer risk (e.g. 1:1,000 at 1.556 mg/m3).

The authors suggest to use the human data, and the committee agree on this decision.

Of note, the data used to assess cancer risk is only based on 1,3-butadiene exposed males, and similar dose-response relations for males and females are assumed. Furthermore linear models are used despite data might be better explained with other functions (figure 2 and figure 3).

Response: It is a common choice to use a linear regression model as starting point for deriving an extra lifetime risk (our approach is the same as DECOS').

For threshold effects, the authors, based on mice data, suggest a DNEL (Derived No-Effect Level) equal to 0.138 mg/m3. Based on the uncertainty for the animal results, most importantly the use of mice with a significant different metabolism of 1,3-butadiene and the uncertainty in the inter-species and intra-species factors, the Committee suggest to put less emphasis on the estimated threshold effects when deciding on the OEL.

The quality committee suggest to use the suggested risk estimate for cancer (leukaemia mortality): 1:1,000 at 3.1 mg/m3, 1:10,000 at 0.31 mg/m3 and 1: 100,000 at 0.031mg/m3 1,3-butadiene.

The quality committee suggest NOT to use the suggested DNEL (Derived No-Effect Level) equal to 0.138 mg/m3 1,3-butadiene.

Response: The current working group do not agree that the uncertainty in the inter-species factor counters for the severity of possible adverse effects related to the human reproductive system. We do believe that our calculation of a health-based exposure limit based on ovarian atrophy in mice in the original report are rather conservative since intra-species uncertainties have not been taken into account due to the stringent approach recommended by ECHA. We fully acknowledge that data show that mice produce more epoxides, especially DEB, than humans during the metabolism of 1,3-butadiene. We have therefore, in the revised report, added a DNEL calculation where we include additional uncertainty factors as well as the inter-species difference in terms of DEB blood levels. This approach results in an approximately similar DNEL as the one calculated in the original report.

References

Bond JA, Csanády GA, Leavens T, Medinsky MA. Research strategy for assessing target tissue dosimetry of 1,3-butadiene in laboratory animals and humans. IARC Sci Publ 1993;127:45-55. PMID: 8070886

Cheng H, Sathiakumar N, Graff J, Matthews R, Delzell E. 1,3-Butadiene and leukemia among synthetic rubber industry workers: exposure-response relationships. ChemicoBiological Interactions 2007;166(1-3):15-24. doi:10.1016/j.cbi.2006.10.004

DECOS. Dutch Expert Committee on Occupational Safety, Health Council of the Netherlands, 1,3-Butadiene; Health –based calculated occupational cancer risk values,2013. No. 2013/08.

Doerr JK, Hollis EA, Sipes IG. Species difference in the ovarian toxicity of 1,3-butadiene epoxides in B6C3F1 mice and Sprague-Dawley rats. Toxicology 1996;113(1-3):128-136. doi:10.1016/0300-483x(96)03437-3

Georgieva NI, Boysen G, Bordeerat N, Walker VE, Swenberg JA. Exposure-response of 1,2:3,4-diepoxybutane-specific N-terminal valine adducts in mice and rats after inhalation exposure to 1,3-butadiene. Toxicological Sciences 2010;115(2):322-329. doi:10.1093/toxsci/kfq060

IARC. 1,3-Butadiene, Ethylene Oxide and Vinyl Halides (Vinyl Fluoride, Vinyl Chloride and Vinyl Bromide). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Volume 97. Lyon, France: WHO; International Agency for Research to Cancer, 2008.

IARC. Chemical Agents and Related Occupations, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Volume 100F. Lyon, France: WHO; International Agency for Research to Cancer, 2012.

Kirman CR, Albertini RJ, Sweeney LM, Gargas ML. 1,3-Butadiene: I. Review of metabolism and the implications to human health risk assessment. Critical Reviews in Toxicology 2010;40 Suppl 1:1-11. doi.:10.3109/10408444.2010.507181

Kirman CR, Grant RL. Quantitative human health risk assessment for 1,3-butadiene based upon ovarian effects in rodents. Regulatory Toxicology and Pharmacology 2012:62:371-384. doi:10.1016/j.yrtph.2011.11.001

NTP, 1993. NTP technical report on the toxicology and carcinogenesis studies of 1,3-butadiene (CAS No. 106-99-0) in B6C3F1 mice (inhalation studies). National Toxicology Program, Research Triangle Park, NC, NTP TR 434.

Owen PE, Glaister JR, Gaunt IF, Pullinger DH. Inhalation toxicity studies with 1,3-butadiene. 3. Two year toxicity/carcinogenicity study in rats. Am Ind Hyg Assoc J 1987;48:407-413. doi:10.1080/15298668791384959

Recio L, Steen A, Pluta LJ, Meyer KG, Saranko CJ. Mutational spectrum of 1,3-butadiene and metabolites 1,2-epoxybutene and 1,2,3,4-diepoxybutane to assess mutagenic mechanisms. Chmico-Biological Interactions 2001;135-136:325-341. doi:10.1016/s0009-2797(01)00220-4

Sathiakumar N, Brill I, Leader M, Delzell E. 1,3-Butadiene, styrene and lymphohematopoietic cancer among male synthetic rubber industry workers--Preliminary exposure-response analyses. Chemico-Biological Interactions 2015;241:40-49. doi:10.1016/j.cbi.2015.09.003

Soeteman-Hernández LG, Bos PMJ, Talhout R. Tobacco smoke-related health effects induced by 1,3-butadiene and strategies for risk reduction. Toxicological Sciences 2013;136(2):566-580. doi: 10.1093/toxsci/kft194

Swenberg JA, Bordeerat NK, Boysen G, Carro S,Georgieva NI, Nakamura J, Troutman JM, Upton PB, Albertini RJ, Vacek PM, Walker VE, Sram RJ, Goggin M, Tretyakova N. 1,3-butadiene: Biomarkers and application to risk assessment. Chemico-Biological Interactions 2011;192:150-154. doi: 10.1016/j.cbi.2010.10.010

Walker VE, Meng Q. 1,3-butadiene: cancer, mutations, and adducts. Part III: In vivo mutation of the endogenous hprt genes of mice and rats by 1,3-butadiene and its metabolites. Res Rep Health Eff Inst 2000;92:89-139. PMID: 10925840

Wallace WHB, Kelsey TW. Human ovarian reserve from conception to the menopause. PLoS ONE 2010;5(1):e8772. doi:10.1371/journal.pone.0008772

Wickliffe JK, Herring SM, Halberg LM, Galbert LA, Masters OE, Ammenheuser MM, Xie J, Friedberg EC, Lloyd RS, Abdel-Rahman SZ, Ward JB. Detoxification of olefinic epoxides and nucleotide excision repair of epoxide-mediated DNA damage: Insights from animal models examining human sensitivity to 1,3-butadiene. Chemico-Biological Interactions 2007;166:226-231. doi:10.1016/j.cbi.2006.04.017