

COLLECTIVE EXPERT APPRAISAL: SUMMARY AND CONCLUSIONS

Related to the development of a Toxicity Reference Value (TRV) for
1-chloro-3-nitrobenzene (meta-chloronitrobenzene)
(CAS No. 121-73-3)

AFSSET Solicited Request No. 070057

Only the French language version of this document shall prevail.

Overview of the question

On 12 November 2007 the Directorate General for Health (DGS) requested that AFSSET develop toxicity reference values (TRVs) for the ortho-, meta- and para- isomers of chloronitrobenzene (CNB), following the contamination of groundwater in Alsace, north of Mulhouse, by organic products containing chloronitrobenzene coming from two industrial sites. This document describes the basic evaluation which eventually lead to a TVR **not** being prescribed for M-CNB.

Organisation of the expert appraisal

A preliminary review of this request was conducted by the CES for "Assessment of risks linked to chemical agents" at its meeting on 24 January 2008 and by the Working Group for "Cancer TRVs" on 31 January 2008. At the end of this review, the CES confirmed the importance of giving priority to developing TRVs for the ortho- and para- isomers of CNB by oral route while the relevance of deriving TRVs for the other routes remained to be evaluated. The issue of developing a TRV for meta-chloronitrobenzene was also raised. This isomer is less stable than the other two and therefore comparatively less likely to be produced in a significant proportion.

Three expert members of the WG for "Carcinogenic TRVs" and two expert members of the CES for "Assessment of risks linked to chemical agents" were appointed as *rapporteurs* on 22 February 2008 and 26 March 2009 respectively to review the mechanism of carcinogenic action of CNB isomers so as to determine the nature of the dose-effect relationship (threshold dose or no threshold dose).

AFSSET conducted a detailed analysis of the literature currently available on CNBs and sent it to the *rapporteurs*.

This work was presented for comments to the Working Group for "Toxicity Reference Values", on several occasions: 19 December 2008, 13 February 2009 and 10 April 2009.

This expert appraisal was therefore done by a group of experts with complementary skills. It was carried out in accordance with the French Standard NF X 50-110 "Quality in Expertise Activities - General Requirements of Competence for Expert Appraisals" to ensure compliance with the following points: competence, independence, transparency and traceability.

Results of the collective expert appraisal

Collection of toxicity data

- General toxicity

The general toxicity of meta-chloronitrobenzene (M-CNB) is not fully understood, irrespective of the route and duration of exposure. Few acute toxicity data are available in animals.

- Genotoxicity

The majority of traditional genotoxicity tests are negative *in vitro* and *in vivo*.

- Carcinogenicity

In 1996 the International Agency for Research on Cancer (IARC) classified M-CNB in Category 3 (not classifiable as to its carcinogenicity to humans). The European Union has not classified M-CNB.

No carcinogenicity data were found in the literature. No conclusions can therefore be drawn about the carcinogenic potential of M-CNB, given the limited data available in animals and humans.

Feasibility of developing a TRV for M-CNB

Given the insufficient toxicity data in animals and humans, it is not possible to develop a TRV for this compound.

Furthermore, it is not conceivable to develop a TRV by structural similarity with other chloronitrobenzenes because the genotoxicity and chronic toxicity profiles differ between ortho-chloronitrobenzene (O-CNB) (which is essentially hepatotoxic) and para-chloronitrobenzene (P-CNB) (which is essentially haematotoxic), and are unknown for meta-chloronitrobenzene (M-CNB).

Conclusions and recommendations of the collective expert appraisal

It has not been possible to develop a TRV for M-CNB, for any route of exposure.

The Expert Committee (CES) for “Assessment of risks linked to chemical agents” accepted the report of the collective expert appraisal at its meeting on 23 April 2009 and informed the Directorate General of AFSSET.

Maisons-Alfort, 28 May 2009

On behalf of the Expert Committee (CES) for
“Assessment of risks linked to chemical agents”,

Chairman of the CES

M. Michel Guerbet