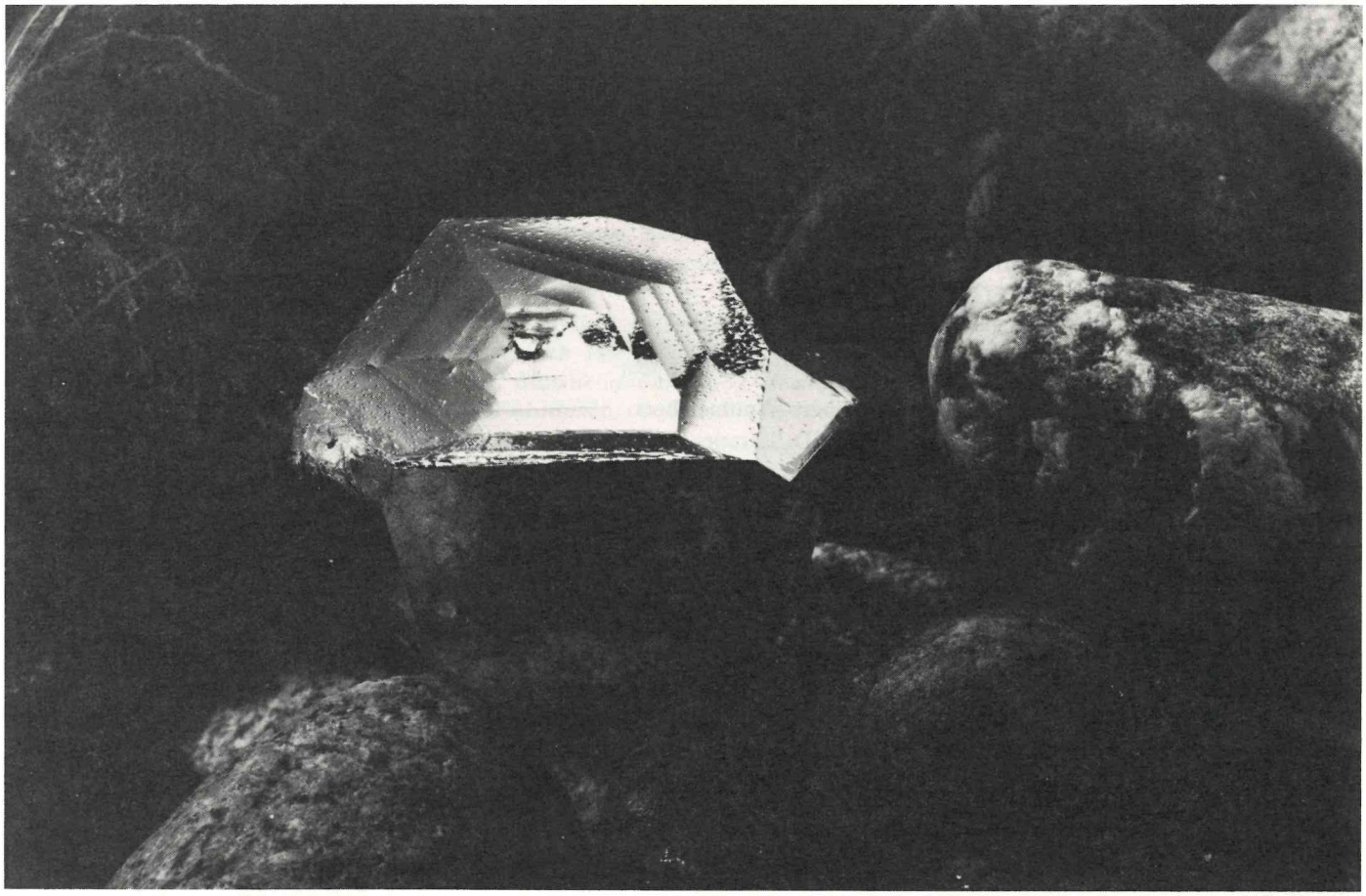

Gallium single crystal (top).

Gallium high purification by partial crystallization (below).

COMMODITY REPORT

The new metals- gallium

By Ulf Bergqvist

The explosive development of new technologies, eg in electronics, optics and computer industries. has rapidly increased the demand for many so called minor metals. A number of these are now of considerable strategic importance to the industrialized countries and are playing an increasingly important role in world trade.
In a series of articles RMR will look at various aspects of these »new metals».
In this issue Ulf Bergqvist introduces the research methodology developed in a major study focusing on the toxicology of the new metals.
He then develops his method by analyzing gallium, an important metal in the semiconductor industry.
In the coming issues of RMR we will look at other aspects of the gallium industry: geology, corporate structure, market and industrial uses.

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INTRODUCTION

Toxicological knowledge on metals and metal compounds is very incomplete. We are gaining an understanding of the major dangers to humans and other organisms of the metal compounds presently in widespread use, but even for those, many uncertainties remain.

One major reason for the slow advance of metal toxicology is the considerable time it takes to detect possible toxic effects of exposure to metal compounds. Toxicological research, once an effect is suggested, is often slow. While research is progressing, further victims and damage due to this alleged toxic effect (if a true one) may occur.

Furthermore, toxicological research utilizes large scientific resources. To investigate in depth all metal compounds presently in use is clearly impossible.

Information enabling us to shorten the time lag between onset of exposure to a metal and recognition of toxic problems associated with this metal exposure would be of value. Some general methods of deciding what metals should be given priority in biological and toxicological research would also be useful.

In this report, one possible approach to this problem is attempted; to arrive at some estimates on present and probable future exposure to various metals and metal compounds – and discuss the amount of presently available information on the possible toxic effects of these metals (compounds).

Thus, while the normal approach when initiating toxicological research (on metal compounds) is and should be based on knowledge (known and/or suspected toxic effects), this complementary approach tries to define our ignorance as a motivation for research – in connection with a measure of 'need to know' by examining exposure.

The methods used means that data are numerically manipulated by various procedures – to achieve a priority order of the metals, based on a certain criterion, without (hopefully) introducing subjective bias. Many different criteria are possible, and a number of these will be presented in this report.

The attempt to avoid bias by using general and numerical methods for all metals means that judgement on special situations for one single metal can not be performed. Thus the information in this report is not complete in the sense that metals not singled out should be regarded as uninteresting–common sense in combination with a specific appraisal of possible toxic dangers associated with a certain metal (compound) is an important primary criterion for determining toxicologically interesting metals. (By doing a limited survey, we can in principle identify only a subset of all 'interesting' metals.) What will be achieved is a list of some 'additional' metals (compounds) which should be given toxicological attention.

This article contains the major results, together with a summary of the discussion on which these results are based. In addition, a detailed scrutiny of one of the metals found interesting by this study, gallium, is presented.

The full report was presented in the USIP series (University of Stockholm, Institute of Physics) in 1983 (USIP Report 83-11). Those wishing to obtain a copy should contact the editor of RMR.

SECTION ONE EXPOSURE TO METALS AND METAL COMPOUNDS A SUMMARY

Fulfilment of purpose:

The purpose of this section was to list interesting metals as regarding exposure. The criteria were developed from three assumptions:

1. A metal (compound) is interesting for toxicological appraisal if the total worldwide industrial consumption is large. Parameters used are *Cons, Dose* and *Toxic.*

Cons reflects the total consumption of

the metal (in moles/year). *Dose* reflects the total consumption of the metal, weighted by the relative abundance of the metal in the human body. *Toxic* reflects the total consumption of the metal, weighted by the occupational hygiene limits for exposure (adjusted for specific compounds).

2. A metal (compound) is interesting for toxicological appraisal if there is a fast increase in its worldwide industrial consumption – especially if the present consumption is small (insufficient practical experience of possible toxic problems associated with this consumption). Some different methods for determining what metals may experience an increased consumption have been utilized. Parameters used are *Prog, Jour* and *Catal.*

Prog reflects the prognosed average annual growth rate up to the year 2000. *Jour* reflects the attention given new technical development based on the metal in certain scientific or technical literature. *Jour* is separated into three different subparameters, based on New Scientist (number of articles, or number of articles weighted by an evaluation of the content of the articles, i e relevance to 'new, probable technology') or Ny Teknik (number of articles).. *Catal* reflects the research emphasis given the metal in research on catalysis (presumably for use in industrial processes).

3. A metal (compound) is interesting for toxicological appraisal if there is a large emission due to the metal being present as a contaminant in other material used (coal, oil etc), or being mobilized from deposits due to other processes (e g acid precipitation). Parameters used are *Oilchem, Oilenv, Coalchem, Coalenv,* and *Acid.*

Oilchem and *Coalchem* reflect the amount of metals in the volumes of oil and coal consumed. *Oilenv* and *Coalenv* reflect these amounts, weighted by the concentrations 'normally' found in soil or sea water (as indicator of natural abundance). *Acid* reflects the degree by which the metal has been included as a factor when studying the effects of acid precipitation. A detailed discussion and a critique of each parameter is found in the full report.

Metals considered

In this report, the word metal will imply the pure metal (or metalloid) and all its compounds, alloys or minerals, unless otherwise specified. Note that the lanthanoids, except for La and Ce, are considered as a group, referred to as Pr–Lu. (Lanthanoids refer to all elements, including La and Ce). The total number of metals considered is 53.

The inclusions of metals in each exposure oriented interest list are subject to availability of data by which parameter values are determined. Exclusion of any metal from a list due to nonavailable data is a serious problem, since these lists are to be used in an attempt to find metals which should be given an increased toxicological attention. (Exclusion implies that information on this metal is scant – but the study was performed in order to try to identify such metals.) A list of English and American names of these metals corresponding to the chemical symbols used in the text is found in Table 4.

Criteria evaluation

Interest lists have been developed for the present world metal consumption as well as the probable increase in world metal consumption – but generally limited to human exposure. No reliable or complete list have been developed for metal exposure from non-industrial sources. The prerequisites for development of these exposure oriented interest lists were:

1. No single criterion for generating an exposure interesting list is considered to be 'best'. Rather several criteria will be defined, and a list will be generated for each – together with a precise definition of the criterion used.

Each criterion used will be given specific motivation, as well as a discussion on its shortcomings. Care must be taken that the criterion definition does cover the total exposure intended.

2. The 53 metals are considered in this report. Data must permit most metals to be evaluated. Metals omitted (not considered due to lack of data) must be clearly stated.

3. The results should be reproducible – avoiding subjective evaluations of criteria fulfillments. In general, this is attempted by basing the criteria on clearly defined numerical parameters.

4. If numerical values are assigned to metals in a 'criteria setting', the scale used may influence the result, if evaluations are based on metals being 'close' or not. The results are therefore expressed only as 'priority groups' for each interest list. Each priority group will contain at least 4–5 metals, the upper limit is somewhat variable in order not to separate metals for which the (imprecise) data can not justify any separation.

5. Computations and selection of values when several are available (and acceptable) are done so that false negatives are avoided, rather than false positives. The motivation for this is that the number of metals found interesting in this section will be further considered and several metals eliminated when evaluating the quantity and quality of toxicological information available. (See also below on reconfirmation).

Fulfillment of these prerequisites by each criterion and parameter definition are shown in table 1. The different exposure settings and organism relevances are shown in fig 1.

The data available as well as the methods used have partially allowed the development of such exposure oriented interest lists. (Note again that the results of this report should be regarded as a complement rather than an alternative to more orthodox methods of deciding pri-

orities for research – see discussion above).

Results of section one

The priority groups arrived at by the use of each parameter are further condensed by the following criteria:

For parameters *Cons, Dose* and *Toxic*

Certain metals were consistently placed in a high priority group. This implies that the total consumption of this metal and its compounds is so high, that the manipulations performed (here) cannot eliminate that metal from a high priority group. A summaric listing of these metals is given:

1. Metals which appear in a high priority group in all parameter applications, and in the highest priority group in at least two studies out of three: Al, Cr, Cu and Fe.
2. Metals which appear in a high priority group in at least two studies out of three, and in the highest group at least once: Ba, Ca, Mn, K, Na, Pb and Ti.

These eleven metals are judged to be the most interecting ones by this criteria – exposure as approximated by world industrial consumption.

A further seven metals appeared inconsistently in a high priority group: Ag, Mg, Ni, Sb, Sn, W and Zn. (Also possibly Ce and Pt).

For parameters *Prog* and *Jour*

Some metals appeared in the high priority groups of both these parameters, and were placed in the highest in at least one: Al, Ga and Ni. Other metals appeared in the high priority groups in both, or were placed in the highest in one of them (excluding those above): As, Ce, Cs, Fe, La, Nb, Pr-Lu and Y.

These two groups of metals should be considered from the point of view of increased exposure in industrial/technical applications.

Some other metals appeared only in one of the highest priority groups in only one of the studies: Cu, Hf, Li, Mn, Mo, Pb, Pt, Ti and Zn.

For reasons discussed above (criteria evaluation), the other parameters were not considered adequate for the study.

The exposure oriented interest lists based on consumption and on probable increase in consumption were subject to reconfirmation in order to eliminate some false positives.

The original computation, on which this 'interest' list is based, was designed to avoid false negatives. The procedure used specific information on the metals in the list.

The result of this reconfirmation was a further limitation of 'interesting' metals. The final results of section 1 are thus:

- **Metals interesting due to high present world industrial consumption:**
Al, Cr, Cu and Fe. To some degree also Ba (?), Mn, Pb and Ti (?).
- **Metals interesting due to a fast (probable) increase in world industrial consumption:**
Al, Ga and Ni. To some degree also Ce, Cs (?), Fe, La, Nb Pr-Lu and Y.

Discussion of results

The 16 metals listed above will be further studied in section 2 of this report – related to the quantity and quality of toxicological information available. Restrictions as to exposure settings and organisms concerned are necessary, since the results have only been obtained for certain combinations (see fig 1).

Thus, in the remainder of this report, the applicability of the results will be limited to humans exposed to metals

Table 1

Fulfilment of prerequisites by criteria and parameters used in section one

Criteria and parameter definition	Reflection of total exposure?[1]	Omissions of metals (% of all metals studied)	Numerical parameter defined?	Fulfilment of prerequisites?
World metal consumption:				
Cons	yes[2]	0	yes	YES
Dose	yes	9	yes	YES
Toxic	yes	8	yes	YES
Increase in world metal consumption:				
Prog	yes[3]	2	yes	YES
Jour	yes	0	yes	YES
Catal	no	0	yes	NO
Sources other than industrial metal consumption:				
Oilchem	no	47	yes	NO
Oilenv	no	47	yes	NO
Coalchem	no	13	yes	NO
Coalenv	no	15	yes	NO
Acid	no	74	no	NO

Notes:

1 Based on assumption of interest, and exposure setting.
2 Complementary parameter definitions (see below for discussion)
3 Complementary criteria definitions (see below for discussion)

handled and emitted from the industrial consumption of each metal. The exposure situation could be occupational or environmental.

Correlations between the results of different studies

Statistical correlations between parameter values for metals in the different studies have been computed. The results are illustrated in fig 2 – with an attempt to graphically illustrate the relationships between different studies.

Apparently, the three different parameters used in the study on technical journals *(Jour)* are closely related, much more so than the different parameters used to describe the present world industrial metal consumption. There is a fairly close relationship between these two groups of parameters, while the relative parameter based on prognosis *(Prog)* is quite apart.

One reasonable explanation for these relationships can be given: The *Jour* studies, especially with paramter values based only on number of articles, do select for new applications of metals, but also with a tendency towards metals with a fairly large (present) consumption. When using a weighted parameter which selects among other things for 'new technology' (New Scientist, weighted) there is a somewhat closer relationship with the *Prog* results. (Note that this weight also contains a factor for 'scale' – favouring relation with *Cons*). (Similar relations exist when examining only the metals in the respective high priority groups.)

Fig 1

Exposure settings and organisms for which results have been obtained

Sources of exposure	Organisms for which results are relevant: Man	Organisms for which results are relevant: Other organisms	Accuracy[1,2]	Bias[1,3]
Industrial consumption	*Cons*[4]		low	low
	Dose		moderate	moderate
	Toxic		high	high
	Jour[4]		moderate	moderate
	Prog		moderate	moderate
	(Catal)[5]			
Other sources	*(Oilchem, Oilenv, Coalchem, Coalenv, Acid)*[5]		Problem: Defining criteria representing all sources	
	Problem: finding representative organism(s)			

Notes:

[1] Subjective evaluation by author.

[2] In defining toxicological interest.

[3] Possibility of bias, largely due to variable extent of knowledge on biological impact of different metals.

[4] General applicability to all organisms.

[5] Studies shown in parenthesis do not fulfil prerequisites, see above.

SECTION TWO
THE EXTENT OF TOXICOLOGICAL KNOWLEDGE AND RESEARCH ON METALS AND THEIR COMPOUNDS

Purpose of this section

The aim of this section of the report is to evaluate the metals found interesting due to present or future exposure situations (section 1). The evaluation shall consider toxicological knowledge presently available, as well as estimate toxicological research activities on these metals.

The result of this evaluation is a new list on 'interesting metals'. It is the opinion of the author, that these metals should be subject to increased toxicological attention.

This section is limited to the effects on humans (and experimental animals) of metal (compounds) used in industry.

Criteria for 'interesting' metals in this section

Evaluation step 1

A metal found interesting in this section does fulfil the following criteria:

- It was found interesting in section 1,
- The research activity on toxic effects is low,
- There is no or insufficient basis to consider this metal inert in biological systems.

A complementary definition of 'interesting' metals is necessary, since the investigation in section 1 fails to detect metals, for which no total increase in consumption is suggested, but where certain new compunds may find increased industrial use. These new compounds may have toxic effects quite different from those hitherto used.

Thus alternative criteria for 'interesting' metals are:

- The industrial use of the metal exhibits a change into certain compounds hitherto not used,
- There is no or insufficient basis to con-

sider this metal compound inert in biological systems.

Evaluation step 2

All metals found interesting by one of these groups of criteria will be subjected to further study, discussing e g the present experience of these metals in exposure situations of interest, etc.

SUMMARY

Fulfilment of purpose

In evaluation step 1, a smaller number of these metals (10) were singled out, for which toxicological research were judged to be 'small' (compared to that of other metals), but which did show some toxic effects in various organisms.

In evaluations step 2, the quantity and relevance of presently available toxicological information was then determined, in order to make possible a final judgement as to the need of further (increased?) research efforts.

A final discussion on the need and urgency of toxicological research on these 10 metals will follow below, but first the criteria used in this section will be briefly evaluated.

Discussion of criteria used

These metals were exposed to four criteria in sequence. (Note the difference between this and section 1, where criteria were used in parallell – being complementary. The four criteria used were:

1. low research activity as estimated by the number of published reports /available in certain relevant data bases/ (parameter *Res).*
2. toxic effects in some different organisms /'biological reactivity'/ (parameter *Spe).*
3. review availability/quantity of information available (parameter *Rev*)
4. relevance of available information /as evaluated by the author/ (parameters *Rel).* A discussion on the performances of these criteria is presented in table 2.

Table 2

Evaluation of criteria and parameters used in section two

Criteria definition	Species used in these criteria	Omissions or not properly evaluated[1]	Numerical parameter defined?	Major technical bias[2]	Major subjective bias[2]	Reproducible
Research activity						
Res	Man and experimental animals[3]	0/16	yes	no	no	yes
Biological reactivity						
Spe	Several of different character	2/10	yes	yes[4]	no	yes
Review availability						
Rev	Man and experimental animals[3]	0/10	yes	yes[5]	no	yes
Information relevance						
Rel	Man and experimental animals[3]	0/10	no	yes[5]	no	no[6]

Notes:

1 No of metals omitted etc/no of metals investigated.

2 Within the criteria; bias which may change relations between parameter values. Technical: due to choice of data and computation procedures. Subjective: due to evaluations by author by use of certain data bases.

3 Largely confined to man and experimental animals.

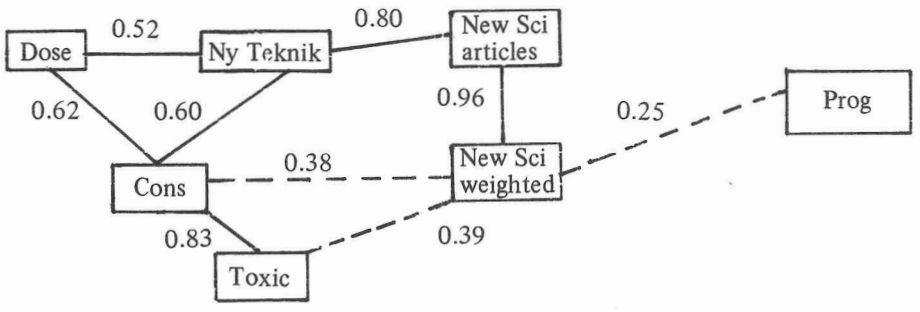
4 Probably, due to choice of organism/system type.

5 Due to information sources.

6 Procedures depend considerably on subjective evaluations by the author.

Fig 2

Statistical correlations between parameter values from different studies.



Criteria and parameters corresponding to the present world industrial metal consumption

Criteria and parameters corresponding to the probable increase in world industrial metal consumption

Legend for fig 2:

For definitions and explanation of *Cons, Dose, Toxic Prog,* Ny Teknik, New Sci/articles and New Sci/weighted see above.

The values given are statistical correlation coefficients between resp parameter value series. Correlations between Ny Teknik and *Prog* was 0.11, and between *Cons* and *Prog* −0.03 (not illustrated).

Results – general description

In evaluation step 1, the 16 metals defined as interesting in section 1 were subjected to criteria *Res* and *Spe* – leading to a reduction in the number of interesting metals. In evaluation step 2, no further reductions were done, but data were aquired which is used in the final description/evaluation of the metals.

In addition, some examples of specific metal compounds (not included in the ten considered above) were discussed: arsenic compounds used in microelectronic industries, certain organic iron compounds, organic ruthenium compounds, metallic tungsten or tungsten carbide and zinc (or maganese) dithiocarbamates. None was judged to be of major interest at present, although the possible introduction of organic ruthenium compounds in industrial use should warrant some further research into e g nervous system effects.

Final evaluation

The results of these deliberations are summarized in table 3.

The choice of individual priorities within table 3 is best left to the reader (as is the choice between these priorities and those arrived at by other methods). The author's view is as follows:

1. Roughly, the more interesting and urgent research needs are displaced towards the upper right hand corner of each row in table 3.
2. Highest priority (P1) and need for general toxicological information (G4) is appropriate for several gallium compounds. (In addition, the partial evaluation possible for gallium salts (G2) should be completed.) See further details and specific motivation below.
3. By using lower priority (P2) and remaining in G4 (need for general information), some attention should be given yttrium and niobium (the information available on these metals is scant, especially on niobium).
4. Some specific research topics (G2) are evident for all lanthanoid oxides, in connection with 'cerium pneumoconiosis'.
5. Some increased information (or at least a more comprehensive literature search) should be gained for organic titanium compounds.

Table 3

Final evaluation of some interesting metals

		Considerable review information available				Little review information available			
		Relevance				Relevance			
		G1	G2	G3	G4	G1	G2	G3	G4
High present consumption	P1								
	P2	Ba[1] Mn[1] Ti[2]			Ti[3]				
Fast increase in consumption	P1						Ga[4]		Ga[9]
	P2					Ce[5] Cs[9]	Ce[6] La[6] PrNd[6]	Cs[7] La[5] PrNd[5]	Ce[8] La[8] PrNd[8] Nb[1] Y[1]

Explanations:

Consumption (present and increae) and review information refer to all compounds.
Review information is highly correlated to some aspects of 'relevance'.
As discussed earlier, this list is complementary to research priorities established by other methods and evaluations.

P1 = highest priority group of the resp measure
P2 = second highest priority group of the resp measure.
G1 = available information makes some evaluation possible as to risks in occupational environments. Specific questions may still be unresolved.
G2 = available relevant information is limited, but some (preliminary and/ or partial) evaluation can be made. Further research for confirmation etc are needed.
G3 = the information, while consierable, was not relevant to or sufficient for a risk evaluation.
G4 = the information was neither of sufficient quantity nor of relevance

Notes:

1 all forms
2 not organic compunds
3 organic compounds
4 inorganic salts
5 halogens and other salts
6 oxide
7 noncaustic compounds
8 metal and alloys
9 arsenide, metal and oxide

Table 4

English and American names of chemical elements

Aluminum/Aluminium	Al	Erbium	Er	Lanthanum	La
Antimony	Sb	Europium	Eu	(Lanthanoids)	La-id
Arsenic	As	Fe	(see iron)	(Lanthanons)	La-id + Y
Barium	Ba	Gadolinium	Gd	Lead	Pb
Beryllium	Be	Gallium	Ga	Lithium	Li
Bismuth	Bi	Germanium	Ga	Lutethium	Lu
Calcium	Ca	Gold	Ge	Magnesium	Mg
Cadmium	Cd	Hafnium	Hf	Manganese	Mn
Cerium	Ce	Hg	(see mercury)	Mercury	Hg
Cesium/Caesium	Cs	Holmium	Ho	Molybdenum	Mo
Chromium	Cr	Indium	In	Na	(see sodium)
Cobalt	Co	Iridium	Ir	Neodymium	Nd
Copper	Cu	Iron	Fe	Nickel	Ni
Dysprosium	Dy	K	(see potassium)	Niobium	Nb
				Osmium	Os
				Palladium	Pd
				Platina	Pt
				Potassium	K
				Praseodymium	Pr
				Promethium	Pm
				Rhenium	Re
				Rhodium	Rh
				Rubidium	Rb
				Ruthenium	Ru
				Samarium	Sm
				Sb	(see antimony)
				Scandium	Sc
				Selenium	Se
				Silver	Ag
				Sn	(see tin)
				Sodium	Na
				Strontium	Sr
				Tantalum	Ta
				Tellurium	Te
				Terbium	Tb
				Thallium	Tl
				Thulium	Tm
				Tin	Sn
				Titanium	Ti
				Vanadium	V
				Wolfram/Tungsten	W
				Ytterbium	Yb
				Yttrium	Y
				Zinc	Zn
				Zirconium	Zr

Fig 3

Stepwise evaluations performed in section two

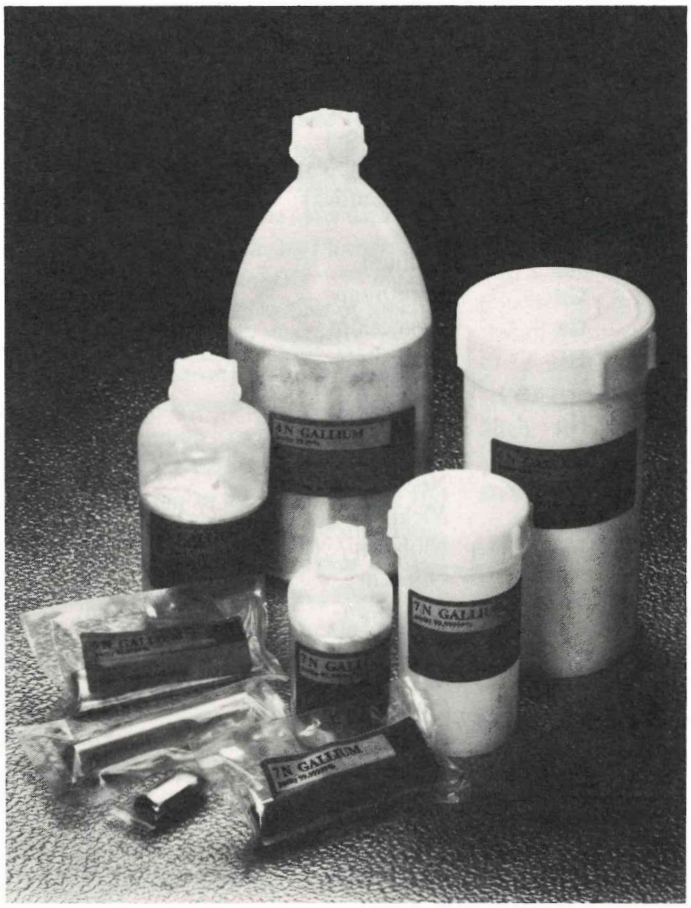
Metals interesting due to large (present) industrial consumption	Metals interesting due to fast (probable) increase in consumption
P1: Al, Cr, Cu, Fe P2: Ba?, Mn, Pb, Ti?	P1: Al, Ga, Ni P2: Ce, Cs?, Fe, La, Nb, Pr-Lu, Y
RES ↓	
P1: – P2: Ba?, Mn?, Ti?	P1: Ga P2: Ce, Cs?, La, Nb, Pr-Lu, Y
SPE ↓	
P1: – P2: Ba?, Mn?, Ti?	P1: Ga[1] P2: Ce, Cs?, La, Nb[1], Pr-Lu, Y
REV ↓	
P1: – P2: Ba?, Mn?, Ti?	P1: Ga P2: Ce, Cs?, La, Nb, Pr-Lu, Y
Considerable information in reviews	Little information in reviews
REL ↓	
P1: – P2: Ba?, Mn?, Ti?	P1: Ga P2: Ce, Cs?, La, Nb, Pr-Lu, Y

Note:

[1] Ga and Nb could not be evaluated by SPE, due to insufficient information. They are therefore retained.

4-7N Gallium products, casted in the form of bottles and ingots (left).

Gallium arsenide is increasingly important in the manufacture of components in the semiconductor industry (right).



Gallium – an introduction

A more comprehensive treatise is given for gallium than for the other metals found 'interesting'. Motivations for this are:

1. Of those metals for which toxicological data are limited or nonexistant, gallium exhibits at present the fastest increase in consumption.
2. Knowledge on gallium – while incomplete – do permit some limited conclusions as to what risks may be involved in gallium industrial exposure. Specific directives for some further research can be stated, data from which would enable us to make a more definite appraisal of gallium in some work environments.
3. The author did not find any (recent) published appraisal or review on gallium toxicology, and had at hand most reports written on gallium in the last years – due to the personal interest of the author.

Gallium chemistry

Many gallium forms such as phosphates, oxides or metal are very insoluble in neutral water. Dissolution of soluble salts will result in the precipitation of e g gallium hydroxide. (In biological fluids, strong insoluble complexes are formed with phosphates.)

Solvation of the gallium ion can be accomplished by making the solvent strongly acid, or by using certain chelating agents such as citrate or EDTA[2,4,37]. Chemical similarities with iron do exist, and gallium binding to (normally iron carrying) transferrin appear to be of major importance in gallium body distribution and cellular uptake[7,15,18,28,35,48,50].

The similarities with iron, magnesium, and calcium have given rize to some theories on possible effects of gallium in the body[6,16,36,44].

- **Metallic gallium**

This gallium form is liquid at 30°C, but the vapour pressure above liquid gallium is very low. The metal does not easily oxidize, owing to the formation of a thin protective oxide layer[55].

- **Gallium arsenide**

The use of this compounds is based on important semiconductor properties. Its chemistry is incompletely known, it oxidizes at high temperatures only, and is apparently brittle[55].

- **Three methyl gallium**

This compound is used in some production processes for gallium arsenide. It oxidezes rapidly and spontaneously in air (inflammable)[55].

- **Gallium oxides**

They exist in several modifications with different chemical properties[55].

The industrial use of gallium

Gallium use in industry has earlier been very limited. The use of gallium and gallium compounds in electronic displays (watches, pocket calculators etc) have resulted in a increased gallium consumtion. The ongoing introduction of gallium arsenide as semiconductors does result in a substantial increase in the gallium consumtion. (Recently, a new gallium production plant was started in France, raising the world production capacity by a third.)[12,17,39,41,42,49,56].

Gallium compounds of major industrial and medical use

Gallium is used in several chemical forms, the most important (and fastest increasing) being gallium arsenide as a semiconductor material.[26,42].

Gallium metal is used in the production of solid-state devices, as a mirror coating and in various alloys (with vanadium, nickel, indium-tin or magnesium)[42].

Radioactive gallium citrate is used in diagnosis of certain cancers and some other diseases[8,13,22,30,31,40]. Gallium nitrate has been tested as a possible anticancer agent[1,5,9,16,23,45,46].

One important method for producing gallium arsenide is by combining three methyl gallium and arsine (vapour phase epitaxy)[17,47]. Other intermediates in gallium arsenide production are gallium chloride (acid) and gallium metal[42,55].

Gallium exposure in certain industries (author's evaluation)

The rapid change in the use of gallium in semiconductor production motivates a survey of possible gallium exposure during the processes used. Little solid data do however exist – and the following description must be considered preliminary only.

Extreme demand on the purity of the gallium arsenide production (by e g vapour epitaxy method three methyl gallium and arsine) makes rigorous control necessary. This control is also motivated by the instability of three methyl gallium in open air, and to the use of arsine. Laboratory scale experience have resulted in few overt problems of exposures – limited to the exhanging of tubes containing arsine or methyl gallium ('obnoxious smell' do sometimes occur).

In liquid phase epitaxy, gallium arsenide is produced from gallium metal in less confined apparatus. The vapour concentration above a liquid gallium surface should be very low. (Whether any operation could produce droplets/aerosols from such surfaces is not known to the author.)

Handling of brittle gallium arsenide could conceivably be a cause of skin contamination.

Microelectronic industries are supposed to have very clean occupational environments, due to demands on purity of products. Recent epidemiological data from California[34] do however call for some caution in relying too much on such general conclusions.

In summary, explicit dangers of continuous gallium exposure in gallium-arsenide production and handling appear to be low. Exposure to gallium may, however, occur due to accidents or to the inappropriate handling of finished material. The amounts used are depending on whether substrates (Ga-(Al)-As base on which the 'doped' material is situated) are manufactured or not.

(The author has not evaluated gallium metal or methyl gallium production.)

Gallium distribution in the body after industrial exposure (author's evaluation)

The following is based on the assumption of exposure to gallium in the microelectronic industry being:

- inhaled gallium compounds in short-term, high level exposure (due to accidents etc): gallium metal or gallium oxides
- possibly long-term, low level inhalation exposure: gallium metal
- skin contact: gallium arsenide

Based on these assumptions, some 'informed guesses' as to body distribution can be made:

Respirable gallium oxide particles will probably largely remain in the lungs, and sufficient amount will then be detectable by x-ray examination (pneumoconiosis, i e the presence of foreign opaque material in the lungs).

(Gallium oxide particles entering the gastro-intestinal tract will not be absorbed to any large extent.)

The fate of metal gallium (in droplets/aerosols) or gallium arsenide (in skin) can not be stated with any degree of certainty. For gallium metal, arguments supporting both a local and a more systematic deposition can be made.

Toxic effects of gallium in man and other organisms

Studies on gallium toxicity have been made both in man and in experiemental animals, but almost exclusively with intravenous injections. The most common and major effect seen is found in the kidneys. Lethal doses (injected slowly) normally cause death by renal intoxication.

- **Kidney damage by gallium salts in man**

If more than about 10–25 mg/kg body weight of gallium salts is injected in man, signs of renal failure are fairly common. Signs commonly noted are proteinuria and azotemia (excessive urea or other nitrogen compounds in the blood). Changes in creatinine clearance have also been detected[9,32,33].

38 cancer patients received doses

above 10–25 mg/kg. 11 developed kidney failure, 5 did recover from these kidney effects, 2 had partial recovery and 4 died of the kidney disorder. One of the fatal cases showed extensive damage to the kidney tubules and the glomeruli at autopsy[9].

Gallium kidney toxicity in experimental animals: Similar effects on kidneys have been seen in several animal species after injection of gallium salts[21,38]. It appears that smaller animal species are less susceptible to kidney damage (doses per body weight needed to be higher to develop kidney damage)[21].

A partial (suggestive) explanation for these kidney effects is the development of precipitates (renal stones) in the kidney tubules. These precipitates consists of calcium, gallium and phosphates, and may completely block many tubules – causing tubular obstruction and thus interfering with kidney function[38].

Gallium apparently serves as a component of these precipitates, but do also appear to increase the urinary passage of calcium, and thus increasing the calcium available for precipitation. This suggestion does, however, not account for all kidney effects seen[21,38].

- **Respiratory effects**

In one reported experiment, an aerosol of gallium chloride caused haemorrhage and other lung damages in exposed rats. In order to keep the gallium chloride in solution, the aerosol was made strongly acid, and the effects seen have been attributed to the acidity of the aerosol[20]. No other reports on pulmonary exposure, neither in experimental animals nor in man have been found. Thus we have no information on the possibility of pulmonary effects after long-term, low-level exposure.

Immediate acute respiratory paralysis have been observed after rapid injection of gallium salts in some animals[21]. No explanation of this (often transient) effect was given.

Intraperitoneal injection of gallium nitrate to mice and rats have produced inflammatory reactions in the lungs, e g in the interstitium. Few details are available on these effects, however[1,29].

- **Blood effects**

In humans and in experimental animals, injected gallium have in some cases produced changes in the blood content of hemoglobin, thrombocytes, leucocytes and neutrophiles. Negative studies have, however, also been reported.[9,29,33,45,46,56].

- **Effects in other organs and system**

Patients have in a few cases developed mild hearing loss. Photophobia and blindness have been reported in rats.[9,20,45,46].

Mild gastrointenstinal effects (nausea, vomiting and some diarrhea) have been noted in humans given gallium nitrate intravenous injections[9,23,45,46,56].

Some skin effects (e g a macropapular rash) have also been after gallium compound injections[46,56].

Oral exposure of rats did not produce any toxic effects even at fairly high doses[21,56]. Gallium salts are presumably precipitated as hydroxides or phosphates in the intestinal tract, thus becoming 'inert' and poorly absorbed.

The regulation of gallium in the working environment

There are no specific restriction on gallium or its compounds in the working environment in e g USA, West Germany or Sweden. A few Soviet reports have been published, where attempts at evaluating gallium in the work environment were made[24,25].

TLV for 'inert dust' should be applicable to gallium oxide or gallium alloy articles. If arsine is used in producing gallium arsenide, the TLVs of arsine are applicable – and actions taken to limit arsine exposure would also tend to limit gallium (compound) exposure in these processes.

Evaluation of possible toxic effects of gallium in work environments:

- **The possibility of kidney damage**

The doses required to produce kidney damage by gallium salts appear to be much higher than those expected in occupational exposure. If all gallium compounds in inhaled air were to be quickly transferred to the blood, a concentration of the order of 50 mg/m^3 air may produce kidney damage. In reality, the air concentrations would probably have to be much higher.

Thus, adherence to existing TLVs on 'inert dust' (10 mg/m^3 total dust – e g USA and Sweden) would protect against kidney damage by gallium compounds in inhaled air. Expected exposure levels in microelectronic industry are not likely to cause any kidney damage. In principle, reservation for metallic gallium is in order – due to lack of data.)

- **Other noted effects**

Effects of intravenously administered gallium compounds are not well characterized, but do apparently depend on fairly large doses. They are (provisionally) judged less likely to occur in microelectronic industries due to inhalation.

No data exist on which to evaluate the possibility of pulmonary effects of inhaled gallium compounds. The probable pneumoconiosis may be benign or malign. (Historical parallells with aluminium and beryllium vs barium and tin are instructive – but do not form any basis for evaluation.)

Gallium appearing in low doses in blood do accumulate to some degree in bone – and especially in growing zones[19]. Whether this has any toxocological significance is not known.

Present research activity on gallium toxicology

Present research into (possible) toxic effects of gallium is almost nonexistant. Of 91 articles of biological interest which appeared in Current Contents/Life Science in 1982, 51 per cent were devoted to scintigraphic use of gallium-67 in tumor diagnoses. A further 40 per cent were related to an understanding of gallium up-

take and body/cell distribution – directly related to these scintigraphic investigations.

Six (7 per cent) articles reported on clinical trials etc with gallium as an anticancer drug. These articles contain some direct information on toxic effects (mainly to the kidneys).

SUMMARY OF SOME RESEARCH NEED

There is a need for certain additional information concerning gallium in industrial occupational health, especially on:

- Do inhaled gallium compounds accumulate in the lungs and if so, is this accumulated material inert or not?
- Is there a risk of forming metallic gallium droplets, and whats the exposed body's distribution of gallium in this form? Whats the possible toxic implications of this?
- Is there any toxicological significance to the noted bone accumulation of gallium?
- Do any skin effects appear after local application of gallium compounds – especially of gallium arsenide?

Answers to these questions would enable some evaluation as to gallium in occupational health: It is entirely possible that the result of such evaluation would be that gallium is not to be considered any real work environment problem. On the other hand, this information would also enable us to more quickly identify work environment problems connected with gallium and its compounds, should such appear.

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